ANNUAL REVIEW OF MEDICINE

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VOLUME 7

1956

ANNUAL REVIEWS, INC.
STANFORD, CALIFORNIA, U.S.A.

ANNUAL REVIEWS, INC.
STANFORD, CALIFORNIA, U.S.A.

FOREIGN AGENCY

Maruzen Company, Limited
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PREFACE

For the present volume, as in the past, we have been fortunate in obtaining the welcome cooperation of writers who, expert in their respective fields, have provided thoughtful and useful reviews of important advances in selected areas of medical knowledge. With great pleasure, we hereby express again our gratitude to those authors who have contributed to the *Annual Review of Medicine.*

It is hoped that this volume and future ones, although addressed primarily to clinical investigators and teachers of medicine in its broad sense, may also prove of value to those fortunate physicians who continue to be medical students.

We cannot close without thanking Mrs. Mary Jean Van Peborgh, Mrs. Delores G. Ward, and other Editorial Assistants who have relieved us of so many burdens.

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VIRUSES OF THE UPPER RESPIRATORY TRACT[1]

By George Gee Jackson

Associate Professor of Medicine and Preventive Medicine, University of Illinois College of Medicine, Chicago, Ill.

The influence of tissue culture techniques, especially the serial propagation of various cell lines *in vitro* as suspended cell cultures, upon our knowledge in the field of infectious diseases and in particular virology, promises to be comparable to the development of semisolid media for the propagation of bacteria. Just as the latter innovation ushered in a period of great attention to etiologic identification, laboratory diagnosis, and taxonomy of bacteria, the use of tissue cultures has already provided a glimpse of a similar prospective era for viral diseases. In this context the subject of viruses of the upper respiratory tract is appropriate for review. Such a title is noncommital regarding the question of the pathologic importance of any particular virus recovered by these new techniques, although commendable epidemiological studies which relate some of the newly recognized viruses to disease entities already have been performed. Neither can this review discuss with any completeness all of the known viruses for which the respiratory tract may serve as a portal of entry, but an attempt will be made to examine the recent contributions to our knowledge of common upper respiratory illnesses and those viruses for which the upper respiratory tract appears to be the principal habitat. Where viral agents have not been cultivated successfully from patients with respiratory diseases that are presumed to have a viral etiology, recent clinical observations will be reported. Although the number of such publications is meager compared to those concerned with the laboratory aspects of viruses from the upper respiratory tract, it must be emphasized that the majority of common upper respiratory illnesses still must be classified upon the basis of clinical observations and epidemiology. Also, the broad application of laboratory procedures that deal with the presently known viruses is not yet practical. Repetition of material discussed in the comprehensive review of viral diseases by T. F. McNair Scott in the *Annual Review of Medicine*, vol. 6, May, 1955 (1) will be avoided except to supplement and enlarge upon certain aspects related to respiratory diseases. Also, in agreement with the advice to reviewers of scientific literature recorded by Arnon (2), only material that has been published or presented will be noted. There is an inevitable lag in such communications and the author knows of additional reports of recent and continuing research upon the common respiratory diseases that can be expected to appear in the near future. It is hoped, therefore, that this review will serve the reader by enabling him to integrate some of the current information with past and future publications.

[1] The survey of literature pertaining to this review was completed in July, 1955.

At the outset, attention should be called to some recent publications of general interest with respect to viral respiratory infections. Of particular merit for both the practitioner and the investigator are the monograph of Stuart-Harris on *Influenza and Other Virus Infections of the Respiratory Tract* (3) and the volume on *The Histopathology of the Respiratory Tract in Human Influenza* (4). A book entitled *Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man* (5) brings together some of the accumulated information in this area. Of broader scope are the volumes *Principles of Animal Virology* by Burnet (6) and *Advances in Virology*, edited by Smith and Lauffer (7). Of particular interest also is the initiation of a new periodical publication, *Virology* (8), which it is hoped will bring together representative publications in this rapidly expanding field and thus serve both for communication and as a reference source.

General Prevalence of Upper Respiratory Infections

Among family groups.—Common respiratory illnesses, notably the common cold, have been identified in a variety of surveys as the human infection most frequently causing illness and absenteeism. The carefully conducted studies by members of the Department of Preventive Medicine at Western Reserve University upon 61 families in Cleveland recently have contributed especially to our knowledge of respiratory infections (9). The design of their investigations has minimized some of the factors, such as the lack of memory for minor illnesses or the ages of the persons observed and the variation in the seasonal incidence of respiratory diseases, that can lead to erroneous conclusions; in addition they have included frequent medical examinations of the patients and have employed the facilities of research laboratories. Among the population that has been observed, which included 170 children 15 years of age or less, common respiratory diseases comprised two-thirds of all new illnesses and caused an average of more than six illnesses per person per year. Only 2.5 per cent of these infections were bacterial in origin and another 2.5 per cent were caused by all other known etiologic agents. Thus, 95 per cent of the respiratory illnesses were caused by unidentifiable (viral) agents. At least once per year on the average each person was afflicted with a non-bacterial respiratory infection that produced fever (10). Young male school and preschool children were observed to have respiratory illness most frequently and in terms of general family illnesses they were the greatest risks, both as index and secondary cases; on the other hand, adult women were more susceptible to, and introduced more respiratory infections into the family, than their mates (11 to 14).

Among military personnel.—Epidemic acute respiratory infections continue to be a major problem among the armed forces and are particularly prevalent when military recruits are brought together for training. Observations made by the Naval Medical Research Unit No. 4 at the Great Lakes Naval Training Center during several winters indicated that respiratory infections accounted for three-fifths of the sick calls (15). Although strep-

tococcal infection is known to be a greater hazard among such a population than among persons in civilian life, 70 to 80 per cent of the admissions for respiratory infection throughout the period of January to May were classified as nonstreptococcal and the majority were of proved or presumed viral etiology (15, 16). Studies from some military installations of the U. S. Army, which will be described later, corroborate this high incidence of viral respiratory infection among new recruits (17).

Influence of tonsillectomy upon respiratory infections.—The question as to whether or not tonsils and especially enlarged tonsils increase the frequency of common respiratory diseases is often deliberated. McCorkle and her associates compared the occurrence of respiratory infections among 230 children who had and had not had their tonsils removed, including 26 children subjected to tonsillectomy during the period of the study (18). Appropriate adjustments were made for age and season. Under these conditions the rates for common respiratory diseases were almost identical in the groups of children with and without tonsils. The observations upon the children who underwent tonsillectomy during the period of study are especially interesting. They revealed that the average rate of respiratory diseases among this group of children had been higher than expected for several years before tonsillectomy, and that the excess rate of respiratory illnesses compared with children who did not undergo tonsillectomy continued unaltered after operation. Thus, increased susceptibility to common respiratory infections was a general characteristic of the group of individuals subjected to tonsillectomy, but the presence or absence of tonsils did not appear to be the cause of, nor have a significant effect upon, the increased occurrence of illness. Among recruits, tonsillectomy was observed to alter the character of exudative pharyngitis from streptococcal infection but the presence or absence of tonsils had no apparent influence upon the percentage of positive cultures for streptococci (16), and therefore presumably had little influence upon the nonsuppurative sequelae of streptococcal infections. From these studies frequent respiratory illnesses per se are not sufficient indication for tonsillectomy, nor an effective prophylactic measure against such infections.

Undifferentiated Acute Respiratory Disease (ARD)

Clinical description.—"Somewhere in the no-man's land between epidemic influenza and the common cold lies a group of febrile upper respiratory infections that are not normally epidemic" stated a recent editorial (19). Similar descriptions of the spectrum of common respiratory infections often have been echoed and a variety of names has been assigned the various clinical illnesses. A syndrome insidious in onset in which sore throat and cough were more prominent than those that accompanied infection with influenza virus was named "febrile catarrh" in 1938 by Stuart-Harris, Andrewes & Smith (20).

During World War II the Commission on Acute Respiratory Diseases of

the Army Epidemiologic Board carried out a series of studies carefully designed to establish suitable criteria for classifying the common forms of respiratory disease that occur among military recruits. They described a febrile respiratory infection of short duration with constitutional and pharyngeal symptoms that differed from the clinical picture of the common cold or influenza virus infection, but which was nonbacterial in origin, and occurred in regular epidemics during the winter months with no significant variation in the clinical illness from one year to another (21 to 24). This illness was referred to as undifferentiated Acute Respiratory Disease or ARD and was likely the same disease as "febrile catarrh." The results of human transmission studies established the etiologic identity of ARD and its immunologic specificity from the agents of the common cold and primary atypical pneumonia of the type associated with cold agglutinins (25, 26).

Isolation of an ARD virus (RI-67).—Refinement of methods (27, 28, 29) for propagation *in vitro* of normal tissues from different species in which cultivation of viruses could be accomplished, and the application of the stable strain HeLa (Gey) of human cancer cells in continuous culture for the isolation of cytopathogenic viruses (30, 31), led to the next major accomplishments in defining the clinical syndrome of ARD. As noted by Scott in the *Annual Review of Medicine* (1), Hilleman & Werner (32, 33) recovered an agent cytopathogenic for human adult tracheal epithelium in tissue culture from the throat washings of a patient with clinical primary atypical pneumonia (PAP). The newly isolated agent was identified by the label RI-67 and it was shown to have the characteristics of a virus. Four additional cultures of virus were obtained in the same epidemic from the throat washings of 29 patients two of whom also had primary atypical pneumonia clinically without cold agglutinins in their sera and two had clinically typical ARD. The strains were readily propagated in HeLa cells, for which they were cytotoxic. This availability of methods for the easy cultivation of RI-67 permitted serological study of the epidemic of respiratory disease at Fort Leonard Wood, Missouri, which involved the patient from whose throat washings the agent first was isolated. Complement fixing antibody against RI-67 was demonstrable in the sera of patients with clinical ARD and PAP by the end of the second week after clinical illness. Neutralizing antibody also increased in the sera of these patients after the 21st to 30th day of the disease. Comparative serologic studies against RI-67 with paired sera from patients with other types of respiratory diseases were negative and indicated the diagnostic reliability of the serologic tests. Influenza A prime virus also was present at the peak of the epidemic, but dual infections appeared to occur in less than 5 per cent of the patients who were studied. These findings further verified the independent identity of the agent RI-67 and its etiologic importance in Acute Respiratory Disease among recruits.

Relationship of ARD and RI-67.—The conclusive link between the clinical syndrome ARD, as described during World War II by the Com-

mission on Acute Respiratory Disease (21 to 24) and the virus RI-67 that was recovered in 1952-53 by Hilleman & Werner (32, 33) was forged from tests upon stored sera from the donors and recipients who had participated in the human transmission experiments conducted 10 years previously and upon the sera from patients who had been ill with ARD at that time (34). Sera from the donor whose illness was classified as ARD and from another whose illness was classified as "bronchitis resembling atypical pneumonia" showed a significant increase in antibody for RI-67. Twenty of 24 volunteers who received the ARD inoculum and 7 of 9 who were challenged with the "bronchitis" secretions had rises in antibody titer for RI-67 in the convalescent phase serum. From similar studies upon the sera from other patients, RI-67 was shown to have no etiologic relationship to the common cold or PAP of the type associated with cold agglutinins. Thus the Commission on Acute Respiratory Disease had accurately done what Andrewes and Stuart-Harris (20) also had claimed, that is, on the basis of clinical observations they had defined a respiratory infection which was a specific disease distinct from influenza, primary atypical pneumonia, and the common cold. The acuity of their clinical observations and the benefit derived from the availability of stored selected serum specimens which enabled such clear-cut results significantly advanced our knowledge of ARD after the isolation of RI-67, which is at least one of the etiologic agents of this syndrome.

Adenoid Degeneration (AD) Agents (Adenoidal-Pharyngeal-Conjunctival Agents)

The recognition of latent viruses in tonsils and adenoids.—At the same time that RI-67 was being isolated another group of workers at the National Institutes of Health was cultivating a variety of human and animal tissues in tissue culture for the purpose of identifying and propagating yet unknown viruses that cause respiratory diseases. Explants of human adenoid tissue that were placed in plasma clots and cultured in roller tubes usually grew well during the first week of culture with epithelial and fibroplastic outgrowth (35). During the second and third weeks of culture, however, characteristic degeneration of the epithelial cells occurred in 33, or 62 per cent, of the adenoids that were observed. The culture fluid from 14 of these degenerated adenoids was transferred to new nondegenerating adenoid tissue cultures and in all except one instance degeneration of the fresh culture was produced. Subsequent passages proved that the agents recovered from human adenoids were cytopathogenic for epithelial cells from a wide variety of human and animal sources; they were nonbacterial, and had the characteristics of a virus, and could be propagated serially in epithelial cancer cells, strain HeLa. Commendation is due these investigators for their perception of the meaning of the spontaneous degeneration of their cultures and for the careful way in which they studied the cellular degeneration and differentiated it from the effects produced by some other known viruses. As will be noted

later, their description of the predominance of nuclear changes in the infected cells was especially accurate. The importance of the contribution of "unmasking" latent viruses (36) from tissues, even those containing specific antibody (37), by the technique of placing in tissue culture the native tissue in which the viruses are present although not recovered by conventional techniques, cannot be appreciated now, but it looms as an important steppingstone to the discovery of many new viruses.

Adenoidal-pharyngeal-conjunctival (APC) agents.—In contrast to the chronologic observations that fell into place with regard to ARD (beginning with the description of the clinical illness, progressing to the isolation of a virus from a patient with a similar disease, and culminating in the serologic proof of the etiologic importance of RI-67), the importance of the new AD agents with respect to clinical illnesses was not immediately apparent. Huebner *et al.* (36) have referred to this situation—the isolation of a virus prior to identification of the human disease it produces, if any—as a "backdoor approach" to the study of respiratory diseases caused by unclassified viruses and they have defended certain advantages in this approach. In their studies it was soon apparent that cytopathogenic agents could be recovered from the tonsils and adenoids of a majority of patients from whom these tissues had been removed surgically (38). More than 100 strains of viruses were readily obtained, many of them from the inoculation of HeLa cells with nasopharyngeal or conjunctival secretions or feces of patients with acute respiratory diseases. Therefore the broader name, adenoidal-pharyngeal-conjunctival (APC) agents, was recommended for these viruses (36, 38) as more accurately describing the principal sources of their origin. The existence of different immunologic types among these agents was demonstrated by serologic cross-neutralization tests. On this basis approximately 85 per cent of strains could be designated in one of six serologic groups. The virus RI-67, previously related to ARD, was found to share some common antigens with the APC agents and became the prototype virus of the serologic type 4. It is of interest that viruses of the types 3 and 4 have been isolated almost exclusively from the secretions of patients with respiratory diseases. On the other hand, strains belonging to the serologic types 1 and 2, which have been isolated from the majority of excised tonsils and adenoids that have been studied, have rarely been recovered from the secretions of patients with acute respiratory disease. Strains belonging to types 5 and 6 so far have been infrequent in either type of material. Although there was some heterotypic response among the different types to immune rabbit antisera which were prepared, and also to immune human serum, the neutralizing titer was nearly always $>1:20$ for the homotypic strain and $<1:5$ for heterotypic virus; humans who became infected showed a fourfold or greater rise in serum neutralizing antibody for the types with which they were infected and a much smaller rise against heterotypes. Hence the immunologic classification seems to merit credence. In contrast to the specific serologic identity of the agents by neutralization test, all of the six serotypes shared common

complement-fixing antigens, suggesting that the different types nevertheless are members of one family.

Pharyngoconjunctival Fever

Whether there are any significant clinical differences in the kinds of illness caused by different strains among the APC-RI-67 family of viruses, and whether or not such differences as there might be parallel the immunologic groups as they are presently constituted, must await additional epidemiologic studies. One clinical variant of the ARD syndrome that deserves special mention is the occurrence of febrile pharyngitis and conjunctivitis. Evidence has been compiled for the person-to-person communicability of such an illness in an epidemic form and its association with an APC type 3 virus (39, 40, 53, 63). The descriptive name pharyngoconjunctival fever was suggested for the entity by Bell *et al.* (40). As has been shown with other common respiratory illnesses (11, 42, 43, 44), children of the grade school ages are most susceptible and adult females appear to be more susceptible than males of equal age (40, 53, 63). In the study of families in Cleveland approximately one-half of susceptible children, that is those without pre-existing antibody in their serum, who were exposed to the disease became ill whereas only one-eighth of susceptible adults who had a known contact with the illness became infected (53, 63). The study of outbreaks in the metropolitan Washington, D. C. area in the summer of 1954 indicated that the incubation period was 5 to 9 days. Among the chief clinical features, fever occurred in 90 per cent, conjunctivitis and sore throat each in about two-thirds of patients, and all three together in approximately one-half of the cases. The conjunctivitis was commonly monocular, nonsuppurative, lasted from one to three weeks and did not produce any pathologic change in the cornea (39, 40). Abdominal pain for one to five days has sometimes been prominent in outbreaks of illness associated with APC-3 virus(es).

Bell and his associates (40) studied 382 persons with acute upper respiratory illness, believed to be pharyngoconjunctival fever, and another 588 persons who were household or close contacts of the afflicted persons. APC-3 virus was found in the secretions from 80 (43 per cent) of 186 persons who were ill and was not recovered at all from 84 persons without illness whose secretions were tested, many of whom had intimate contact with clinical cases. Of those in whom the virus was isolated from the eye swab, 91 per cent had definite conjunctivitis; but only 68 per cent of patients with conjunctivitis yielded a positive virus culture from the eye. Thus virus isolations were closely associated with the occurrence of clinical disease and also related to the conjunctivitis. In addition, serologic studies for antibody showed a significant increase between the paired sera from 20 of 22 persons from whom virus was obtained. Other observations indicated that virus was commonly present during the acute stage of the disease and for limited periods before and after the onset of illness. The period of communicability was assumed to be about 10 days.

Related New Agents and Clinical Entities

Roseola infantum.—The isolation of a cytopathogenic agent by Neva & Enders (45) that induced nuclear degeneration in human epithelial cells from an infant with fever, conjunctivitis, and skin rash also was noted in the *Annual Review of Medicine* (1). It is of interest that this agent has been shown to have the antigenic characteristics of an APC-3 virus (36). The patient from whom the strain was isolated had the clinical syndrome of pharyngoconjunctival fever with the additional variation of a maculopapular skin eruption over the shoulders and chest. At the time of the patient's illness, however, an epidemic exanthematous disease associated with a serologically different agent or agents was prevalent and one cannot assign the production of the rash to the APC-3 agent with certainty.

Keratoconjunctivitis.—Epidemic keratoconjunctivitis is a disease that has been observed to occur in epidemic form similar to pharyngoconjunctival fever (46). Also, the disease is usually monocular. In contrast to the findings of Bell (40) regarding APC-3 disease in which there were no corneal lesions, the acute conjunctivitis of keratoconjunctivitis is followed after a few days by keratitis and the formation of subepithelial corneal opacities. Previous reports have related the cause of this affliction to St. Louis encephalitis virus (47) and herpes simplex (48). The recent report of Jawetz and his associates (48) concerning two cases of typical acute keratoconjunctivitis is very important. An APC agent was recovered from the first patient and a significant rise in antibody titer for this agent was observed in the sera of the second patient who was his nurse. No APC agent was recovered from scrapings from the eye of the second patient but herpes simplex virus was isolated; however, this cannot be accepted with certainty in a laboratory where herpes simplex from other sources is under study (49) and the latter view regarding the origin of the virus might be supported by the lack of a serologic antibody response to the herpes virus. Despite this the question remains as to whether keratoconjunctivitis might be a dual infection involving an APC agent or whether some strains of the latter family might be a sole cause of the disease.

Swimming pool conjunctivitis and Greeley disease.—Several reports in past years (50, 51, 52) have called attention to small epidemics of a clinical syndrome similar to that noted in this review as pharyngoconjunctival fever. During the past year serologic study of paired sera, stored from persons observed during an outbreak at Greeley, Colo., has related the etiology of the syndrome reported by Cockburn (52) rather conclusively to an APC-3 agent (36).

Other ARD viruses.—There are unquestionably additional agents cytopathogenic for HeLa cells which might cause respiratory infections clinically indistinguishable from ARD of known etiology. Huebner and his colleagues (36) have observed patients who showed an increase in complement fixing antibody for antigens that are common to the APC agents without showing a rise in neutralizing antibody for any of the six prototype viruses already

known, thus indicating additional immunologically distinct members within this family. Ginsberg *et al.* (53) studied epidemics of ARD in three military installations in which serologic tests indicated the disease commonly was caused by agents antigenically unrelated to RI-67 or the AD viral agents. Also viral pneumonias of the types with and without cold hemagglutinins in the patients' convalescent sera were unrelated serologically to APC viruses. Berge and his associates (54) isolated 45 agents that were cytopathogenic for HeLa cells from the throat washings of 157 patients with a variety of clinical respiratory infections, of which 17 viruses were immunologically similar to RI-67 and two were unidentifiable. Still other, yet unrecognized viruses may multiply within cells without giving rise to easily discernible morphological or biochemical changes (55, 56).

Relationships of the New Agents and Respiratory Disease

Clinical epidemiology.—While it seems reasonably well established that RI-67 and APC-3 respectively are causally related to acute respiratory disease (ARD) and a similar illness commonly associated with conjunctivitis, there are still many aspects of the clinical inter-relationships between these two agents and between them and the other AD agents that require clarification. In some epidemiologic studies of APC-3 induced illness nearly all of the persons in any age group who were infected, as shown by virus isolation or by a specific serologic response, were clinically ill (40, 53). Ginsberg *et al.* (53) found clinically recognized cases mainly among children, and observed that adults with serologic evidence of infection frequently had no associated illness. Epidemiologic investigations with RI-67 among a company of 209 recruits observed at Fort Dix, New Jersey during the winter months showed that 81 per cent had serologic evidence of infection with the RI-67 family of viruses, but among the infected group 43 per cent did not report symptoms of respiratory illness, 28 per cent were treated at the dispensary for respiratory symptoms, and only 29 per cent were confined with an acute respiratory disease (17, 57). Experiments with human volunteers to whom virus had been given via the respiratory tract and parenterally also have shown that infections can be produced frequently without any evidence of illness (17, 36).

Conjunctivitis has been present in approximately one-half of the recognized illnesses associated with APC-3 virus and varies in different epidemics (39, 40, 52). The most common epidemiologic factor among cases with conjunctivitis appears to be swimming; this might indicate the route of infection rather than any characteristic of the strain. Active virus has not been recovered, however, from chlorinated swimming water that was suspected of viral contamination (40), and conjunctivitis has occurred in patients without a history of swimming or immersion (39, 48).

Future consideration will have to be given to determining the influence of dual viral infections, since influenza virus (32, 33), herpes simplex (48), Coxsackie virus (40), the common cold (36), and possibly an agent of roseola

infantum (45) have been associated with the newly identified respiratory viruses during illness. Also in a single epidemic more than one immunologic type of APC agent has been active (53, 62).

Serologic epidemiology of the new respiratory agents.—As previously noted, the various types of AD viruses and RI-67 share common antigens that are demonstrable by a complement fixation test. These antigens are soluble and can be separated from the infectious unit by centrifugation (38). The serologic response as measured by complement-fixing antibodies is almost entirely nonspecific for viruses within the APC family although the titer may reflect how recently the infection occurred. The antigens are produced by few or no other infectious agents; thus the complement-fixation test provides a means by which recent infection or previous experience with the APC agents can be detected (36). Neutralization tests performed in tissue culture, on the other hand, provide a test for antibody that is for the most part type specific, although the sensitivity and specificity of the test are influenced by the procedures used (38, 55). Neutralizing antibody persists in the serum for years. Eighty-eight per cent of spontaneous human infections were found to cause an eightfold or greater increase in complement-fixing antibody and at least a fourfold increase in neutralizing antibody for the agent isolated from the patient. The latter increase may be specific or nonspecific as to the immunologic type of the virus, but an eight- to sixteenfold increase in neutralizing antibody is almost certainly type specific (36).

With these serologic tests it was possible to obtain information regarding the prevalence of prior infections within various population groups and to observe the relationships between antibody and host susceptibility. Sera obtained from clinics in the Washington, D. C. area showed that more than 50 per cent of infants six to eleven months of age had neutralizing antibody against one or more types of APC viruses (36). A progressive increase in antibody occurred with age so that the majority of persons aged 16 to 34 had neutralizing antibody for three or more of the six types tested. Other studies indicated that infection with different types continued to occur well beyond the age of 34. Studying another civilian population, Jordan (61, 62) found no neutralizing antibody for RI-67 in the sera of 73 children, whereas 17 per cent of mothers and 53.7 per cent of fathers or approximately 35 per cent of 84 adults' sera collected in 1954 had neutralizing antibody for this agent. The difference between men and women could not be related to previous military service of the fathers. More than three-fourths of the persons with antibody in their serum were found to have had it when their serum was first collected, more than five years previously. These findings are interpreted as indicating that infection with RI-67 seems to have been prevalent in the community prior to 1948, but it has not caused infections within recent years among the families under study. This conclusion was corroborated by the study of paired sera from another 58 adults who had had recent acute respiratory illness. Of these persons 34 per cent also had neutralizing antibody for RI-67 in their serum and 36 per cent had similar antibody for an

APC-3 virus. After the respiratory illness 19 per cent of the persons had an increase in neutralizing antibody to an APC-3 agent or RI-67 in their serum, but two-thirds of the patients who showed a rise in serum titer to RI-67 had had contact with this virus in the laboratory. On the other hand, ARD associated with the APC-3 agent appeared to be occurring spontaneously in the community at the time these studies were conducted and it was responsible for about one-fifth of the cases of nonbacterial pharyngitis observed among a group of Cleveland families (61, 62).

Among military recruits, however, RI-67 (ARD) infection has been prevalent in recent years (17, 32, 33, 57). As noted previously, 81 per cent of a group of recruits studied during the winter at Fort Dix, New Jersey, and 10 per cent of a group observed during summer months had serological evidence of infection with the RI-67 family of viruses. Survey of selected sera from patients with ARD at Army installations in different sections of the United States indicated that the RI-67 group of agents was very prevalent at five of these stations (17). At Fort Ord, California, 157 of 201 observed cases of acute respiratory illness were nonbacterial and noninfluenzal. Forty-three strains of (ARD) viruses were isolated and 40 per cent of them were immunologically like RI-67 (54). The results of tests for RI-67 complement-fixing antibody in the sera of military personnel and their dependents who were sick with nonrespiratory illnesses, with observations covering age groups from infancy to 70 years, led Hilleman and his associates (17) to conclude that the greatest prevalence of infection was during mid-life (ages 17 to 30 years) with fewer infections in infancy and older adults.

Influence of antibody upon the susceptibility to infection.—Susceptibility to clinical infection induced by a bacterial-free filtrate of throat washings obtained from a patient with ARD has been related by Ginsberg and his colleagues (53, 62, 63) to the presence or absence of circulating RI-67 antibody prior to infectious challenge. Among 24 volunteer subjects, 94 per cent of those who had no antibody in their preinoculum serum became ill, whereas only 38 per cent of persons who had antibody in their preinoculation serum showed signs of clinical illness. These studies permit the interpretation that susceptibility to infection with ARD is positively correlated with the absence of specific neutralizing antibody. The presence of antibody, however, does not insure resistance to clinical infection. This conclusion is borne out by other human volunteer experiments (36). Thus, the protective effect of circulating antibody is probably related to the serum titer and the strength of the challenge, as well as the specificity of the antibody. Supplementary to these studies the authors (53) observed an outbreak of nonbacterial pharyngitis involving 31 persons in 12 families in which an APC-3 virus was prevalent and two strains of an "AD-2-like" agent was isolated. Serum specimens were available also from 61 well family members. In this outbreak resistance to infection did not appear to be related to the presence in the serum of antibody for the "epidemic strains." Of 22 persons who became ill and who showed an increase in serum antibody titer, however, none had

neutralizing antibody for the current strains in the acute phase serum. Among recruits Hilleman (17) found that RI-67 complement-fixing antibody in the initial serum specimen did not materially influence the incidence of infection with the RI-67 group of viruses.

Infection with nonpathogenic APC agents?.—The question of pathogenic or saprophytic existence of strains among this recently identified family of viruses is one that will require continued attention for many years to come. The epidemiologic and immunologic evidence that has been reviewed establishes beyond question the pathogenic importance of some strains of these newly recognized respiratory viruses. The present status is reminiscent of a similar concern with regard to pneumococci and streptococci before serologic typing, or to staphylococci before the coagulase test helped to define the strain differences. To extend the bacterial analogy there may be important differences also with regard to the tissue or secretion from which the agent can be recovered, similar to the different meanings of alpha streptococci in the throat and in the blood of a patient with a cardiac murmur, or between *E. coli* in the stool and urine. Some helpful suggestions for conducting investigations in viral disease have been proposed (49, 64, 65).

There are a few instances in the recorded experience that suggest an occasional "fellow-traveler" role, sometimes complete with antibody response, for the APC virus. Such a role for an APC-3 virus was recognized by Huebner and his associates (36) during the serial passage in human volunteers of secretions from a person with an afebrile, nasal discharge type of common cold. During the serial passage of "colds" in volunteers the APC-3 agent was acquired and disappeared from the secretions used for challenge without altering the nature of the induced "cold." These authors also isolated an APC-3 virus from lung and mesenteric lymph node tissue obtained at autopsy from a case of Letterer-Siwe disease in which its etiologic importance is quite dubious. The AD agents types 1, 2, 5, and 6, despite the fact that they commonly can be "unmasked" and isolated from excised tonsils and adenoids, rarely have been established conclusively as the cause of any illness. The hypothesis that they contribute to chronic disease of the tonsils is an interesting one but as yet it is unproved (37). In a few instances APC viruses (types 1 or 6) have been obtained from persons with respiratory illness who have not had an increase in antibody for the isolated agent. Certainly the role of the APC agents in keratoconjunctivitis, if any, requires further study. As Dubos (66) has said in his challenging article upon unsolved problems of infectious diseases " . . . the determinants of disease are not the same as the determinants of infection," and investigation of the precise mechanisms by which these viruses cause disease is greatly needed.

Properties of the APC Viruses

Biological and physical characteristics of the viruses.—Many properties are common to the different immunologic types of APC viruses. All of them are epitheliotropic and produce extensive cytopathic changes in tissue cul-

tures of epithelial cells that have originated from a variety of sources and different species, among them the human epithelial carcinoma cell, strain HeLa (56). The adsorption of virus upon HeLa cells, however, is rather slow and incomplete. There is a lag of 19 to 24 hr. before appreciable multiplication of the virus occurs. The cells in an infected culture become enlarged and rounded. The cytoplasm at the periphery of the cell remains clear, but the nuclei become large and granular and clumped masses of cells form and are sloughed from the vessel wall (35, 36, 38). The characteristics of the cytotoxicity produced in HeLa cells by the AD agents and the RI-67 viruses differ, according to Ginsberg & Gold (67). The latter authors described the degeneration with the AD agents as productive of a round mass of cell material in which the identifying membranes of the individual cells cannot be made out, whereas these cell outlines characteristically persisted when RI-67 was the infecting agent. Supravital staining revealed that in contrast to poliomyelitis and some other cytopathogenic viruses the cytopathic cell was not necessarily killed. The APC viruses can produce hyperplasia of the infected cells rather than cell death, and an increased utilization of glucose with increased production of lactic acid is characteristic of an infected HeLa cell culture.

Rapid multiplication of virus occurs in infected tissue cultures and the maximum titer of virus may be obtained before complete degeneration of the tissue culture occurs. A study of the yield of virus obtained from infected HeLa cell cultures indicated that the virus was not readily released from its intracellular position into the fluid culture medium, and even after marked degeneration of the tissue culture the majority of virus particles remain intracellular (67). The soluble complement-fixing antigens, however, are present in large amounts in the culture medium.

Some properties of the APC viruses have been tabulated by Huebner and his colleagues (36) and their findings are reproduced here in Table I. As noted, none of the agents has shown appreciable pathogenicity for a variety of laboratory animals. The viruses are relatively stable at room and refrigerator temperatures and Ginsberg (67) observed RI-67 to be more stable than the AD agents at 50°C. All of the strains studied were inactivated quickly at 56°C. The viruses also are quite stable to variation over the range pH 3 to 9. Additional biophysical properties of RI-67 have been noted by Hilleman and his co-workers (68). From ultrafiltration studies the virus particle was judged to be 80 to 120 mμ in diameter and the complement-fixing antigen(s) 26 to 40 mμ in size. The virus diameter calculated from sedimentation coefficients and an assumed density of 1.104 was 114 to 115 mμ.

Electron microscopy.—HeLa cell tissue cultures infected with RI-67, APC-3, and an AD agent have been studied under electron microscopy by at least three groups of investigators (68, 69, 70). All of the investigators agree very closely on the pathologic morphology in the infected cells. Within 20 to 48 hr. virus-like particles were visualized only in the nucleus. After

48 hr. numerous particles spherical in shape [50 mμ×30 mμ (70); 40 mμ diameter (69); average 97 mμ diameter (68)] were arranged in the nucleus in crystalline-like patterns. The nuclei subsequently appeared to disintegrate and a few irregular granules appeared in the cytoplasm, but the cytoplasmic structure of the cells with nuclear particles appeared largely unchanged. None of these changes was observed in uninfected HeLa cell cultures. On a morphologic basis the newly recognized family of respiratory viruses are intranuclear viruses. From the number of particles in the infected cells apparent in the electron photomicrographs, one might expect a higher tissue culture infectivity titer from the harvest than has been found by most workers and it may be that many of the particles seen are noninfectious.

Antigenic variation.—Throughout this review the newly recognized viruses have been referred to as a family of viruses and also as the AD

TABLE I

SOME PROPERTIES OF ADENOIDAL-PHARYNGEAL-CONJUNCTIVAL VIRUSES*

1. Production of unique cytopathogenic changes in:
   —human explant cultures (epitheliotropic)
   —HeLa cells, with acid production
   —monkey kidney
   —rabbit trachea
2. Apathogenic for laboratory animals
3. Ether resistant
4. Heat labile (56°C. for 30 min.)
5. Filtrable (sintered glass, Mandler)
6. Resistant to antibiotics
7. Type-specific neutralization
8. Group-reactive complement-fixing antigens and antibodies (not type-specific)
9. Soluble antigen

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family, the RI-67 family, and the APC family. With the present status of our knowledge it seems most appropriate to continue to identify the various strains as closely as possible with their derivation. Evidence for antigenic variation among the RI-67-like viruses has been presented by Hilleman and his associates (57, 71). Ginsberg and co-workers (53) recovered an "AD-2-like" and an APC-3 virus in a single outbreak of acute respiratory infection and still were unable to demonstrate an increase in neutralizing antibody for either of these agents in 24 per cent of the persons who were ill simultaneously (62). It will take some time to gain an understanding of the number of antigenic constituents in the composition of these newly recognized viruses and to determine the rate at which antigenic variation occurs. This possibility of diversity among strains will require consideration in future epidemiologic and investigative studies with regard to these viruses.

Other Upper Respiratory Viruses

The common cold.—"I have long been satisfied from observation that people catch cold from one another when shut up together in close rooms and coaches, and when sitting and conversing so as to breathe each others' transpiration; the disorder being in a certain state." This quotation given in a recent editorial and attributed to Benjamin Franklin approximately 185 years ago portrays the opinion of scientists and laymen alike that the common cold is a common contagious disease that has been transmitted from person to person for centuries. An average of 2.2 common colds per year was found among 131 office workers in London who recently were observed weekly throughout one entire year. There was a sharp epidemic of colds which coincided with a sudden fall in outside temperatures and humidity and at the same time there was a notable increase in the prevalence of streptococci. Most investigators, however, believe the common cold is a specific entity caused by a specific virus(es). Gohd recently reviewed the literature of the subject (74). The most recent and probably best description to date of the characteristics and properties of the common cold virus(es) has come from the researches of Andrewes and his associates carried on at the Harvard Hospital, Salisbury, England (75, 76). The infective agent may be stored two years or more at −76°C. The size of the particle is less than 70 mμ and perhaps as small as 30 mμ in diameter. It is unaffected by the antibiotics that are currently available, but the virus is inactivated by drying and by 20 per cent ethyl ether. The human infectivity titer of nasal secretions may reach 10^3 but has been found to be less than 10^4 infectious doses per ml. At any one time, however, approximately one-half of the persons who are challenged with such secretions will not have symptoms of infection. The susceptibility of individuals is of primary importance and in the case of experimental challenge it is not influenced by the season of the year, the time since the most recent natural cold, nor by a chilling environment. Observations regarding the increased susceptibility of adult females, the incubation period (two to three days), the symptoms, and severity of colds induced among volunteers are in agreement with some epidemiologic observations by other workers (78, 42, 43). The similarity of results strengthens the evidence that the clinical common cold also is a reproducible and definite syndrome.

The announcement of successful propagation of the cold virus in tissue culture of embryonic human lung by Andrewes (82) has not yet been confirmed, to the author's knowledge, in other laboratories and has not yet yielded the tools—reproducible serologic identity, cytopathogenicity for tissue cultures, characterization, titration, and neutralization of virus, electron microscopy, etc.—that are so necessary to a further understanding of the common cold virus(es). A recent report indicated that the investigators in Salisbury, England, had been working with a new strain of common cold virus that produced a higher proportion of colds among volunteers (83). The incubation period was longer than that previously observed. Nasal discharge was abundant and very little general malaise was produced.

Attempts to grow the common cold virus in embryonated eggs have continued in some laboratories. Pollard & Diserens (84) have reported an abnormal cytological response apparent in the allantoic fluid of embryonated eggs following inoculation with secretions from persons with a common cold. Approximately two-thirds of the secretions were infective as judged by the induction of allantoic fluid pleocytosis. The fluid from eggs inoculated with these secretions had 40 to 500 histiocytes per oil immersion field, whereas normal eggs had 0 to 34 cells. The exudative effect also was demonstrable in serial passages of the fluid. The response was eliminated by heating the secretions before inoculation, and by specific antisera (rabbit), but not by pooled human gamma globulin. This interesting technique will require additional study and confirmation to relate the pleocytosis conclusively to the presence of virus. The criterion—increased cells in the allantoic field—is nonspecific and it is quite likely that some factors other than virus also are involved. Gohd (85) has grafted human adenoid tissue to the chorionic epithelium in preparation for attempts to propagate the common cold virus in transplanted human tissue. In approximately one-half of the eggs he observed hyperplasia and metaplasia of the entodermal epithelium lining the allantoic cavity. If the adenoids that produced this reaction were infected with AD agents, and it is likely that more than one-half of the tissues used were infected, the observations may lend some strength for the viral origin of the pleocytosis reported by Pollard & Diserens (84).

Despite the slow accumulation of facts and the frequent lack of reproducible results, the circle defining the common cold is steadily constricting and its definition has received considerable impetus from several significant contributions within the past few years.

Influenza.—The influenza virus literature was brought up to date in the *Annual Review of Medicine*, Vol. 6 (1). The disease is not primarily an upper respiratory infection either by symptomatology or histopathology (4) although coryzal symptoms may dominate the clinical picture at some localities during certain epidemics, "trivial influenza" (3).

Recent editorials have restated our knowledge of the cyclic nature of influenza epidemics caused by A and B type viruses and the uncertainty of their clinical differentiation (86, 87, 88). Within recent years influenza B outbreaks have predominated in the United States and England (89, 90). It is apparent from recent studies that strains of influenza B virus are showing the same kaleidoscopic variation in antigenic composition that has been shown for A type virus (91, 92, 93). Influenza C virus, the type most recently recognized is much more likely than types A and B to produce an afebrile illness, with nasal congestion and sore throat, which occurs commonly in infants and children and in sporadic outbreaks (94 to 97).

The studies of Davenport and co-workers (98) that related the character of the antibody in the pooled sera of groups of persons at various periods in life to the antigenic composition of the strains of influenza prevalent in these

periods and to the immunity of each group have been extended (99). A comparison of sera from England and the United States showed the British specimens to be markedly lower in antibody for A and A-prime viruses, and the authors believe the finding explained the relative severity of an outbreak of influenza in England and the mildness of a simultaneous outbreak with the same antigenic type virus in the U.S.A. Another group of investigators observed that the high serum antibody levels for specific viruses declined to approximately pre-epidemic levels four years after an epidemic (88, 100). The persistence of antibody against older epidemic strains supports the hypothesis that people tend to respond to infection with influenza virus by producing more antibody against the strain which first attacked them rather than the current strain (92, 101).

Recent reports of interest regarding the recovery of influenza virus from throat washings concern the use of human embryonic or monkey kidney cells in tissue culture for the primary isolation of the virus (102, 103, 104). This method was used successfully for all three types of influenza virus and was superior to embryonated eggs for the isolation of influenza B virus. Another study showed no increase in the number of influenza virus isolations following an attempt to liberate antibody-bound virus by the addition of concentrated heat-inactivated virus to throat washings (105).

These various clinical and laboratory studies are bringing closer the time when diagnostic procedures for influenza viral disease can be applied more broadly and appropriately; increasing our understanding of clinical and subclinical cases in the natural spread of the disease; and adjusting our expectations regarding epidemic influenza and the propsects for effective immunologic prophylaxis against the illness. Studies of another nature are defining chemical substances that inhibit the multiplication of influenza viruses with minimal tissue toxicity, and might lead to effective chemotherapy of influenza virus infections and perhaps even chemoprophylaxis during period of epidemic infection (107, 108).

The Coxsackie viruses.—The role of many strains of the group A and B Coxsackie viruses respectively has been rather well-established as a cause of herpangina and epidemic pleurodynia or aseptic meningitis (64). These viruses are among the most common of the known agents that have been recovered from human secretions and raised serious concern regarding the concept of the "normal" viral flora of man. The frequency and nature of the minor respiratory illness, in which fever, nasal symptoms, and sore throat are predominant, and which are accompanied by serologic or virologic evidence of infection with Coxsackie virus, was reiterated by the studies of Melnick, Walton & Myers (108, 109). Unclassified acute minor respiratory illnesses occurred among 31 per cent of children under 10 years of age during August and about 25 per cent of the morbidity was caused by infection with Coxsackie viruses. This corroborates the conclusion of Huebner and his associates (64) that herpangina is one of the most widespread summer infec-

tions of childhood. The review by the latter investigators remains quite complete and representative of the nature and importance of the Coxsackie viruses.

Miscellaneous Viruses

Poliomyelitis virus.—During the past year there have been some additional reports of "minor acute respiratory illnesses" as the major manifestation of infection with one or another of the known viruses that characteristically produces nonrespiratory disease. Horstman and her colleagues had previously shown the occurrence of minor illness, sometimes with respiratory symptoms, among patients infected with poliomyelitis virus (110, 111). Jordan *et al.* (51) recently observed a family suffering from what appeared to be undifferentiated acute respiratory disease during the fall when respiratory illness was common and poliomyelitis was not epidemic. Poliomyelitis virus was isolated from the throat washings of three of six members in the family. Studies with chimpanzee-avirulent poliomyelitis virus in human volunteers performed by Sabin (112) showed that localization and multiplication of the virus in the throat was common but among these persons it did not produce symptoms.

Infectious hepatitis "virus."—An extremely interesting report is that of Chancey & Zatz (113) of an illness which the authors elected to call sporadic acute anicteric hepatitis and which was characterized by acute upper respiratory symptoms and epigastric or liver pain. When first seen, 41 of 43 patients complained of sore throat and had definite objective evidence of pharyngitis, exudative in 17, upon examination. The other two patients had had a respiratory infection during the preceding two-week period. The liver was enlarged in 40 patients; splenomegaly and lymphadenopathy occurred in approximately one-half the patients; bronchopneumonia was observed twice. Pathogenic bacteria frequently were cultured from the throats of the patients. The authors interpreted the subsidence of respiratory symptoms as a response to antibiotic therapy and offered the opinion that the prodromal stage of hepatitis predisposed to upper respiratory infection. Although the authors were conscientious in their attempts to identify the etiology of the syndrome with the tools at their disposal, the nature of the causative agent remains in doubt. During the period of observation 10 cases of icteric hepatitis and 24 proved typical cases of infectious mononucleosis were encountered. It is quite likely that the etiology of the disease is viral, possibly related to the newly recognized group of agents presented earlier in this review, or possibly, as the authors suggest, an atypical strain of infectious hepatitis or infectious mononucleosis "viruses."

Infectious mononucleosis "virus."—Infectious mononucleosis is known to occur as a primary upper respiratory illness which affects young adults principally. Recent reports have been interesting in their attempts to establish the incubation period and mode of transfer of the disease from epidemiologic observations (114, 115). Two studies in which the index cases

were quite definite, placed the incubation period at 4 to 14 days and 32 to 49 days, respectively. Thus, until the tools are available to identify and differentiate the causative agent(s) the conclusions must be tentative. Hoagland's (115) hypothesis that the mode of transfer of infectious mononucleosis is by oral contact, especially intimate osculation with an infected person in the incubation period or with carriers, if such exist, is an interesting one. Its application in disease prevention suggests acquaintance for at least six weeks before one engages in such social customs. The desirability and means of executing such a recommendation is beyond the wisdom of this reviewer.

Primary atypical pneumonia "virus".—Primary atypical pneumonia is another illness which is mentioned here only to call attention to it as having different etiologies from those reviewed earlier (116, 117, 118). In the classical illness cold hemagglutinins appear in the patients' convalescent serum. That other agent(s) still distinct from the RI-67 family can produce a similar syndrome without the development of cold agglutinins is evident from the serologic data of Ginsberg *et al.* (53). Of interest also is the report of a mild respiratory illness, like primary atypical pneumonia, among individuals in a poultry raising area with serologic identification of the agent among the psittacosis-lymphogranuloma agents (119).

Measles virus.—Measles virus is the chief agent producing respiratory symptoms among those that cause the common contagious diseases of childhood but it regularly exhausts the availability of susceptible hosts. The incidence in the United States during the first quarter of 1955, however, was slightly higher than in 1954 and above the five year median (120). Therefore it still ranks high among the viral causes of upper respiratory infections. The report of successful isolation of several strains of a cytopathic agent from the blood and throat washings of patients with measles and serologic evidence to identify them as the cause of the illness (121) further clarifies the pathogenesis of this disease and may present the means to accomplish prophylactic immunization.

Comment

It is apparent, I believe, from the content of the reports briefly reviewed here, which represent only a sample of those that might be considered cogent, that the combination of thought and techniques and the vigor of the activity being lent for a better understanding and delineation of the most common of all man's illnesses—upper respiratory infections—can cause one to be optimistic about a future practical knowledge of these illnesses. The popular clinical diagnosis of "virus infection" or "cold" and the virologist's dilemma of isolated "orphan viruses" without a known disease entity have already begun and will surely continue an amalgamation into congruent patterns of clinical illness with practical laboratory tests to identify them. Concurrently a greater fund of academic knowledge regarding the pathogenesis of viral diseases, including tissue tropism of various viruses and the relationships of antibody and natural resistance to immunity, can also be expected to

accumulate. The era of nomenclature and taxonomy, debate regarding etiologic and epidemiologic importance, and definition of the biologic behavior of the newly recognized viral agents will inevitably be fraught with difficulties, misconceptions, and subsequent contradictions, but this does not mask the significance of recent contributions nor the perception of potential ones to follow.

It might occur to some that this statement of optimism overlooks the omission of a section in the review on the treatment of upper respiratory viral infections and only occasional mention of immunologic prophylaxis. There is very little knowledge of practical benefit with regard to treatment at the present time but these aspects must follow the others and some preventive or therapeutic contributions also are on the horizon. For those who desire a better knowledge of the past experience in the therapy of viral respiratory infections, the controlled study of Cronk and his associates (122) and the recent review by Finland (123) are recommended.

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NUTRITION AND NUTRITIONAL DISEASES

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Frequently the expanse of a subject area is obscured through preoccupation with small, rapidly growing buildings which may obstruct one's outlook. So it is with that area of medicine known as nutrition. The breadth of the subject and the potentialities for application of our knowledge for the betterment of man's health throughout the world remain in striking contrast to the condition of man and understanding of health improvement attainable by the application of existing scientific information. He who attempts to apply knowledge gleaned in the laboratory and medical centers often meets frustration because of the gross ignorance of practical techniques for coping with the human prejudices, attitudes, superstitions, convictions, and traditions in which food—its production, use, and consumption—is bathed. These qualities plague the physician regardless of whether he is advising an individual patient or is concerned with influencing the nutritional policy of a nation.

Of inestimable value, therefore, is the exchange and dissemination of summary knowledge and techniques afforded by numerous official and quasi-official agencies, national and international. The media of exchange of such agencies are ofttimes less widely available than the usual medical journals. Accordingly, this chapter will comprise to a major extent brief references to considerations of importance to many of these agencies. If it leads to a better understanding of the policies of some of these groups and the assistance available from them, it will have served its purpose.

The broadest responsibilities in nutrition are shared by the two United Nations' specialized agencies—Food and Agriculture Organization (FAO) (1) and the World Health Organization (WHO) (2 to 7). In the field of nutrition the former (8) is concerned with advising on the production, processing, and distribution of food, and the latter with the medical problems which arise from food or deficiencies of it. The activities of the two agencies are well-depicted in the reports (9, 10, 11) of the FAO/WHO Joint Expert Committee on Nutrition. The latest report of this Committee (12) highlights the considerations of protein malnutrition and the feeding of infants and children, of educational and training needs in nutrition, of the diseases pellagra and endemic goiter, of fortification of dry skim milk with vitamins A and D, of the assessment of nutritional status (including anthropometry), of the relationship of nutrition to degenerative diseases, and of food additives.

Protein Malnutrition

The subject of protein malnutrition, or kwashiorkor, was admirably reviewed by Davies (13). From the Kampala group there has now appeared an

extraordinarily valuable monograph on kwashiorkor (14). This book is the most complete summary on kwashiorkor which has come to the present reviewer's attention. An excellent section on the history of the disease is followed by a clear account of the natural history, clinical course, differential diagnosis, pathological anatomy, biochemical findings, and prevention and treatment of kwashiorkor. Although the account is based primarily upon the wide experience of the authors with the syndrome as it appears in Africa, every effort is made to correlate the findings with those observed elsewhere. Certain conclusions recorded by these workers deserve reiteration. The syndrome occurs in post-weaning children, usually between the ages of one and two years. All of the clinical signs are not always present in a given case and the signs, which vary in degree, are not well-correlated with the severity of the disease. Considerable agreement as to the characteristics of the syndrome in different areas now appears. The usual syndrome includes edema, skin lesions, hair changes, apathy, retardation of growth, fatty infiltration of the liver, and hypoproteinemia and hypoalbuminemia. Diarrhea or steatorrhea varies, but usually occurs in some stage of the disease. The atrophy of the pancreas, emphasized by Davies (15), is a logical explanation for the decrease in content of amylase in the serum of infants with the disease (16). Oomen (17) has called especial attention to the growth retardation of children with "malignant malnutrition" in Djakarta—a phenomenon observed in other regions as well (18). Much of the present agreement on the syndrome appears to stem from the opportunities for workers from many regions to compare and discuss their observations in person, especially at the conference in Gambia (11, 22) and Jamaica (18). Mortality is high unless proper treatment is given, and some children die suddenly from an unexplained cause despite therapy. It is still held that lack of protein in the diet is the chief cause of the disease, and treatment with vitamins or lipotrophic substances alone fail to alleviate the condition.

Cow's milk continues to be the most satisfactory source of protein for treatment, although mixtures of plant proteins have been used (14, 19). In view of the occurrence of diarrhea in kwashiorkor, often even preceding development of other symptoms (20), it is surprising that so little attention has been given to the possibility of electrolyte imbalance in this disease. Hansen & Brock (21) have observed that, in six cases of postdiarrheal nutritional edema, therapy and improvement was attended by a retention of both potassium and nitrogen. A greater retention of potassium was observed than would be expected from the theoretical potassium-nitrogen ratio of three to one. Indeed, in two cases potassium, administered without protein, was retained, and this retention was associated with a reduction in the edema. Further studies of the electrolyte changes in this state of chronic diarrhea will, no doubt, be fruitful, and adoption of the same therapeutic measures for establishing electrolyte balance as are widely used in other forms of diarrhea may be expected to contribute to a reduction in mortality from kwashiorkor. Another therapeutic adjunct which would appear to

deserve wider consideration than it has received is that of the preventive administration of antibiotics to the child with kwashiorkor. That such might be especially effective is suggested by the knowledge of the relatively unsatisfactory conditions of hospitalization in many places where kwashiorkor is treated and the consequent opportunities for cross-infection to occur.

The names applied to the syndrome of protein malnutrition in infants are legion. "Kwashiorkor" has been widely adopted and, as pointed out by Williams (23), the word means, literally, "the disease the child gets when the next baby is born"—an accurate description of its occurrence. The precedent of similar genesis of other disease names, such as beri-beri or pellagra (24) would seem to constitute ample justification for retention of this descriptive and euphonious name.

The report of the joint WHO/FAO study of kwashiorkor in Central America (25) shows it to be similar to the disease elsewhere. A striking difference lies in the occurrence of the band-like dyspigmentation of the hair which is more readily visible in the straight hair of the Indians than in the kinky hair of the African native. The disease has been well described as occurring among the rice-fed infants of Indonesia (17). Indonesian infants have an unusual incidence of xerophthalmia (approximately 70 per cent of the patients examined). Punch biopsies of the liver of Oomen's cases in Indonesia revealed a high incidence of fatty changes and of fibrosis. Walters & Waterlow (26) report that moderately fatty infiltration of the liver associated with fine periportal fibrosis frequently occurs in malnourished children in Gambia. These changes were not necessarily a portion of the syndrome of kwashiorkor.

The methionine and cystine content of the hair was unchanged in 33 cases of kwashiorkor in Indonesia (27). The dyspigmentation of the hair characteristic of this disease in many areas (28) suggests some derangement in the metabolism of the pigment precursors—the aromatic amino acids. The metabolic interrelation of these and other amino acids with ascorbic acid and folic acid (29, 30) may indicate leads for further study of the phenomenon.

The occurrence of ophthalmia among malnourished children in Indonesia (17, 17a) is a manifestation of avitaminosis A. It is in such areas as this that dried skim milk, fortified with vitamin A, would be a particularly useful product. Many investigators are giving attention to the problem of developing nonmilk sources of protein for use in child and infant feeding in protein-deficient areas. Two valuable reports of such studies are those of Dean (19) and of Widdowson & McCance (31). Dean employed cereal combinations containing barley, wheat, soya, or maize (with or without milk.) Children ranging from newborn to 11 years of age were studied. For children up to one year of age, only about half of the milk in the diet could be replaced by the mixtures, but for those from one to two years of age, certain of the mixtures could completely replace milk. For older children maximum growth required the addition of some milk to the routine cereal diet. Widdowson & Mc-

Cance's study was made on children over five years of age and thus is not strictly pertinent to the problem of kwashiorkor. Nevertheless, it reveals the finding, surprising to some, that wheat flours of 70, 85, and 100 per cent extraction, when constituting 75 per cent of the calories of a low animal protein diet, sufficed for excellent growth and rehabilitation of children. Furthermore, after one year on this diet, growth was not improved by the daily addition of 500 ml. of reconstructed full-cream dried milk for a period of six months. It is apparent that there are grounds for optimism in the effort to develop a suitable cereal mixture to serve as a source of protein in the feeding of children.

Of special pertinence to the future developments in studies of protein needs and economics is the publication by Rose (32) of the last of the detailed reports of the studies on the qualitative amino-acid requirements of healthy young male adults for maintenance of nitrogen equilibrium on a purified diet containing amino-acids in lieu of protein. Demonstrated as essential are valine, leucine, isoleucine, threonine, methionine, phenylalanine, lysine, and tryptophan; and as dispensable, "nonessential" are glycine, alanine, serine, cystine, tyrosine, aspartic acid, glutamic acid, proline, hydroxyproline, histidine, citrulline, and arginine.

In the consideration of predominantly cereal dietaries in protein-poor undernourished areas the quantitative relationship between nonprotein calories and protein (33, 33a) or amino-acid (34) requirement is of special importance. The substitution of wheat-flour protein for the same quantity of amino-acids in a purified diet sometimes converted a definitely negative nitrogen balance to a positive one in young college women (35)—a finding which suggests that this effect may be partly due to unidentified dietary relationships or constituents. Details of the quantitative studies on requirements for young men set the tentative daily minimum intake for L-tryptophan (36), L-phenylalanine (37), and L-lysine (38) at 0.25 gm., 1.10 gm., and 0.8 gm., respectively—identical with the minima proposed earlier by Rose (39). In studies on college women levels of minimal requirements for L-tryptophan, L-threonine, and L-valine of 0.15 gm., 0.20 gm., and 0.55 gm. have been reported (35). These are lower than the minima summarized for young men (39).

Pellagra

Although uncertainty remains as to the incidence of pellagra in many parts of the world, the disease continues to be a significant problem in those regions where maize supplies 60 per cent or more of the calories of the diet (12). The report of the Fourth Joint WHO/FAO Committee (12) notes that pellagra has diminished to the vanishing point in the southern portion of the U.S.A. and in Italy, but that it is prevalent in some regions in Egypt, Yugoslavia, and Basutoland. Since 1940, the disease has been reported from the majority of the countries of Latin America, and from Puerto Rico, Portugal, India, and Southern Rhodesia; a serious outbreak occurred in Spain during

the Civil War (1936 to 1939). A particularly striking account of the disease in Yugoslavia has been provided by Professor Borić (40). Here, the disease is associated with the consumption of stone-ground, whole maize. In Basutoland the disease also persists (41); its peak incidence occurs in the spring months of September to December. Home-grown mealie meal, a whole grain meal produced at hammer mills, is consumed in maximum quantity for the two or three months preceding the outbreak of pellagra. At the time of the maximum incidence of the disease, however, imported mealie meal, partly as refined meal and partly hammer-milled in the territory, constitutes the larger fraction of the maize consumed.

As a result of an earlier study of pellagra in Basutoland in 1947, Waterlow & Webb (42) were struck with the historical association of the occurrence of pellagra in that country with the introduction of the milling technique which led to greater consumption of whole ground maize. Recently attention has again been called to this point (43), but it remains impossible to separate clearly the direct influence of changes in milling practice from those numerous alterations in dietary habits simultaneously occurring in regions where new milling processes reflect economic, cultural, and dietary trends in the countries.

The existence of significant pellagra in a population is clear evidence of bare subsistence-level feeding on a diet of negligible choice enforced by the dictates of poverty. In such situations, the first step in improving nutritional health is "to loosen the grip of poverty. Only when that has been done is there scope for food education" (44). While one may disagree with the complete acceptance of the latter priority, the compromise of nutrition and health imposed by the combination of economic and educational poverty (45) is vastly greater than any single corrective measure which may be conjured up by the naive scientist.

The influence of another maize processing technique, *viz.* the preparation of tortillas, on the incidence of pellagra has continued to receive attention and investigation. There is a prevalent impression that pellagra is less frequent in those areas where tortillas are consumed than would be expected were the same quantity of maize eaten in some other form. Evidence against this impression has been provided by the studies of Goldsmith *et al.* (46), in which three human subjects were maintained on diets containing maize pre-treated with lime (tortilla treatment) and two subjects on comparable diets containing untreated corn. The rate of appearance of the signs of niacin deficiency was identical in the two groups and the rate of decrease in excretion of niacin metabolites was similar. These studies failed to show any influence of the lime treatment of corn upon induction of niacin deficiency. Indeed, from calculations of the niacin-tryptophan intake of a tortilla-consuming population in Central America the workers at INCAP (47) have found that the usual intake of beans supplements the diet sufficiently that the combined niacin-tryptophan intake exceeds the quantity of 190 mg. of tryptophan and 7 mg. of niacin daily which Goldsmith and her coworkers (48)

found to be minimal. These observations, therefore, give cause to question the widespread impression of a beneficial effect of tortilla processing on the reduction of pellagra in man.

On the other hand, experiments in animals (49, 50, 51) continue to indicate that treatment of maize with dilute alkali in some manner decreases the rapidity of development of niacin deficiency. A number of possible explanations include the concept of neutralization of a toxic factor present in maize, the release of "bound" nicotinic acid not available in untreated corn (52), or some other alteration in the composition of the maize. In this connection it is important that Koeppe & Henderson (53) have shown that rats receiving a purified amino-acid diet containing approximately 0.1 per cent of tryptophan develop niacin deficiency when the remaining essential amino-acids are provided at levels expected to give maximum growth. The reduction of the content of threonine, lysine, leucine, isoleucine, and valine was followed by an improvement in growth. This was interpreted as indicating a less severe niacin deficiency, and was in keeping with the concept that tryptophan serves more efficiently as a precursor of niacin when there exists a relative lack of some other essential amino-acid which restricts the amount of tryptophan required for protein synthesis. Indeed, unpublished observations (54) from this laboratory strongly support the view that the effect of alkali treatment on maize can be partially explained by this concept. Eventual elucidation of these interrelationships observable in animals will permit a decision as to whether simple processing techniques should be modified on this nutritional basis. In practice it is important to keep before us the benefits of adding sources of niacin and proteins of supplementary quality to the diet (55).

No biochemical assessment of nutritional level of niacin has proved more satisfactory than the measurement of urinary excretion of N-methylnicotinamide. Evidence is accruing for the presence of additional niacin metabolites in the urine of lower animals (56, 56a), and one of these has been identified as β-nicotinoyl-D-glucuronic acid (57). This substance, however, has not been detected in the urine of man.

Endemic Goiter

The widespread geographical distribution of endemic goiter was extensively documented (58) in 1946. No decrease in the wide occurrence of this disorder has since been noted. The extent of the problem has recently been more clearly defined, however. Outside the capital city of El Salvador the average incidence of goiter was 22.8 per cent, varying from 8.5 to 38.7 per cent in the different departments of the country (59). Similarly, an average of 22.6 per cent of the persons in Honduras were found to have enlarged thyroids (60). The occurrence of the disease in Mexico (61), in India (62), in Yugoslavia (63), in Ceylon and Nigeria (63a), and in Australia, New Zealand, and Melanesia (64) has been presented in recent years. These indicate but a few of the examples of further recognition of the problem and of need

for corrective measures. The most complete recent study of the metabolism of iodine in endemic goiter is that of the Mendoza investigation (65).

All groups which have given attention to the problem of endemic goiter and its prevention have agreed that iodinization is an effective control measure. It is not surprising, therefore, that the Fourth FAO/WHO Joint Committee (12) should have recommended "that WHO should continue to call the attention of governments to the problem of endemic goiter and to the recent advances in its prevention through new methods of iodization of salt." The new method of iodization referred to consists of the addition of iodine to salt as iodate. The reason for use of iodate is that it is stable when mixed with moist crude salt (61, 66, 67, 68) while iodide is readily lost from the crude salt commonly used in most parts of the world.

The evidence indicates that iodate in small quantities is metabolized similarly to iodide and that it has a large margin of safety (61, 68, 69). Finally, weekly administration of 8.5 mg. of potassium iodate to school children in Central America for 15 to 25 weeks was followed by the same reduction in goiter incidence as followed the giving of 6.5 mg. doses of potassium iodide (70). A similar increase in protein-bound iodine of the blood serum was noted in the treated groups.

The possibility of widespread goiter prevention seems now to be within reach (12) with the new knowledge which is accumulating on iodate, coupled with the invention of new equipment suitable to small plant operation for the controlled addition of iodine salts to open-pan and solar evaporated salt (71).

Fluorides

No attempt will be made to review the large recent literature on the use of fluorides in water and the relationship of fluoride ingestion to dental caries. Suffice it to refer the reader to three authoritative monographs (72, 73, 74) which summarize well the development of our knowledge of fluorides in relation to dental health and several practical considerations, including the engineering aspects of fluoridation and the control of fluoride quantity in water supplies. These monographs should prove especially valuable to physicians and health workers who are often called upon to express opinions for the guidance of municipal officials in decisions concerning fluoridation. Indeed, illogical and nonscientific opposition is often encountered to the institution of fluoridation (75) and a reservoir of factual information is the only effective weapon for combating it. As evidence of the opposition it is noted that by the end of 1954, suits had been brought in eleven cities to prevent the fluoridation of city water supplies. Fortunately, decisions of the courts in 11 different states and one appeal which reached the U. S. Supreme Court were favorable to fluoridation programs as adopted by local officials (76). It is apparent that this application of scientific knowledge in nutrition to the improvement of dental health is now proceeding soundly and with acceptance based upon reasoned understanding of the scientific evidence.

Fluoridation will supplement, but not supplant, other dental health

measures (77). About one-half of the population of the U.S.A. lives in small villages and rural areas where fluoridation of public water supplies is not feasible. Accordingly, other provisions for preventing dental caries in this segment of the population must be continued and developed. The Food and Nutrition Board of the National Research Council has provided a comprehensive summary of the work on the nature of other factors of importance in dental health (78). This Board has pointed up the problems arising from the use of vehicles other than water for enhancing the intake of fluorine and has concluded that water is the most reliable vehicle for this purpose and that "other vehicles, liquid or solid, cannot at present be recommended . . . " (79). Adequately controlled studies are called for if any other vehicle were to be entertained as suitable.

Dietary Standards

The 1953 revision of the Recommended Dietary Allowances of the Food and Nutrition Board (80), as shown in Table I, differs from the 1948 revision in several important ways. First, their intended applicability is clearly defined by the complete title "Recommended Dietary Allowances for the Maintenance of Good Nutrition in Healthy Persons in the United States of America." It is implicitly stated that these allowances " . . . are not necessarily applicable to situations of stringency or limited food supply. The recommendations are not requirements, since they represent not merely minimal needs of average persons but nutrient levels selected to cover individual variations in a substantial majority of the population." Although intended to cover needs in times of stress they are stated to be lower than may be needed in pathologic states or in rehabilitation of deficient subjects. They are not designed to provide a basis for judging nutritional status. They do not cover losses in cooking, processing, or storage. The tentative nature of these (and all other!) such standards is clear—the present revision represents the fourth one, and it may be predicted that additional ones will be made in the future.

In this revision, the calorie allowance has been determined by the FAO system (81), adopting a "standard" man and woman, aged 25, living in a temperate climate, weighing 65 and 55 kg., respectively, and fairly active physically. The proper adjustments, therefore, must be applied to the value in Table I to suit the particular use. The smaller "standard" subject is responsible for the seeming decrease in the allowance of protein, but the adult figure has in fact remained at 1 gm. per kg. of body weight.

The recommended intake of calcium for adults has been reduced to a level in agreement with the 1943 allowance. The niacin standard has also been lowered, and minor adjustments have occurred in the recommendations on riboflavin in conformity with the principle of relating this vitamin to the level of protein intake (0.025 × gm. protein = mg. riboflavin). Allowances for the following nutrients were not formulated quantitatively: carbohydrate, fat, sodium, potassium, chlorine, phosphorus, copper, iodine, fluorine, trace

TABLE I

FOOD AND NUTRITION BOARD, NATIONAL RESEARCH COUNCIL: RECOMMENDED DAILY DIETARY ALLOWANCES, REVISED 1953
DESIGNED FOR THE MAINTENANCE OF GOOD NUTRITION OF HEALTHY PERSONS IN THE U.S.A.

(Allowances are considered to apply to persons normally vigorous and living in temperate climate)

	Age, Years	Weight, kg. (lb.)	Height, cm. (in.)	Calories	Protein, gm.	Calcium, gm.	Iron, mg.	Vitamin A, I.U.	Thiamine, mg.	Riboflavin, mg.	Niacin, mg.	Ascorbic Acid, mg.	Vitamin D, I.U.
Men	25	65 (143)	170 (67)	3200*	65	0.8	12	5000	1.6	1.6	15	75	
	45	65 (143)	170 (67)	2900	65	0.8	12	5000	1.5	1.6	15	75	
	65	65 (143)	170 (67)	2600	65	0.8	12	5000	1.3	1.6	13	75	
Women	25	55 (121)	157 (62)	2300*	55	0.8	12	5000	1.2	1.4	12	70	
	45	55 (121)	157 (62)	2100	55	0.8	12	5000	1.1	1.4	11	70	
	65	55 (121)	157 (62)	1800	55	0.8	12	5000	1.0	1.4	10	70	
	Pregnant (3rd trimester)			Add 400	80	1.5	15	6000	1.5	2.0	15	100	400
	Lactating (850 ml. daily)			Add 1000	100	2.0	15	8000	1.5	2.5	15	150	400
Infants	0–1/12‡												
	1/12–3/12	6 (13)	60 (24)	kg. ×120	kg. ×3.5†	0.6	6	1500	0.3	0.4	3	30	400
	4/12–9/12	9 (20)	70 (28)	kg. ×110	kg. ×3.5†	0.8	6	1500	0.4	0.7	4	30	400
	10/12–1	10 (22)	75 (30)	kg. ×100	kg. ×3.5†	1.0	6	1500	0.5	0.9	5	30	400
Children	1–3	12 (27)	87 (34)	1200	40	1.0	7	2000	0.6	1.0	6	35	400
	4–6	18 (40)	109 (43)	1600	50	1.0	8	2500	0.8	1.2	8	50	400
	7–9	27 (59)	129 (51)	2000	60	1.0	10	3500	1.0	1.5	10	60	400
Boys	10–12	35 (78)	144 (57)	2500	70	1.2	12	4500	1.3	1.8	13	75	400
	13–15	49 (108)	163 (64)	3200	85	1.4	15	5000	1.6	2.1	16	90	400
	16–20	63 (139)	175 (69)	3800	100	1.4	15	5000	1.9	2.5	19	100	400
Girls	10–12	36 (79)	144 (57)	2300	70	1.2	12	4500	1.2	1.8	12	75	400
	13–15	49 (108)	160 (63)	2500	80	1.3	15	5000	1.3	2.0	13	80	400
	16–20	54 (120)	162 (64)	2400	75	1.3	15	5000	1.2	1.9	12	80	400

* These calorie recommendations apply to the degree of activity for the reference man and woman described in the text. For the urban "white-collar" worker they are probably excessive. In any case, the calorie allowance must be adjusted to the actual needs of the individual as required to achieve and maintain his desirable weight.

† The recommendations for infants pertain to nutrients derived primarily from cow's milk. If the milk from which the protein is derived is human milk or has been treated to render it more digestible, the allowance may be in the range of 2 to 3 gms. per kg. There should be no question that human milk is a desirable source of nutrients for infants even though it may not provide the levels recommended for certain nutrients.

‡ During the first month of life, desirable allowances for many nutrients are dependent upon maturation of excretory and endocrine functions. Therefore no specific recommendations are given.

elements, vitamin B_6, vitamin B_{12}, folacin, pantothenic acid, biotin, and vitamin K.

Those responsible for feeding hospitalized or institutionalized patients will find the tentative Recommended Daily Allowances for Public Health Service Hospitals (82) of interest. These allowances are generous modifications of the Food and Nutrition Board's recommendations for a physically active male and, to this reviewer, are larger in calories and protein than seems likely to be consumed by most patients for long periods. The relatively high levels of calcium and riboflavin included probably reflects a generous use of milk.

Clinical Appraisal of Nutritional Status

The recent literature continues with rather too numerous papers on the significance, specificity, or meaning in terms of malnutrition of various clinical signs. Few new signs have been clearly linked with nutritional deficiency. One is inclined to agree with Passmore (83) that the 1951 FAO/WHO Joint Expert Committee Report (10) provides an admirable background of our present knowledge of methods of assessing nutritional status.

It would be difficult to imagine attempting an assessment of nutritional status without a proper clinical examination, but when appraisal of the nutrition of populations is made it is necessary to employ dietary surveys, a study of vital statistics, anthropometric measurements, and biochemical and physiological studies, as well as clinical appraisals. In addition, properly designed therapeutic trials are often indispensable. The symposium "Methods for Evaluation of Nutritional Adequacy and Status" (84) provides an excellent bench mark for measuring future progress in this field.

Two signs which deserve some attention are parotid enlargement (85) and leukoedema and keratosis of the buccal mucosa (86). The former has been widely observed by workers dealing with malnourished subjects (87, 88) and may be seen in kwashiorkor (14). The relationship of these changes in the salivary glands to those in the pancreas (15) and to serum amylase concentration (16) may be profitable to study, both in kwashiorkor and in the cases of nonsymptomatic parotid enlargement.

Other Studies

Pantothenic acid deficiency.—Clinical and metabolic changes have been produced (89) in four young men by a combination of feeding a purified diet low in pantothenic acid and daily administration of 0.5 gm. of the antagonist, omega-methyl-pantothenic acid. Changes occurred within two weeks following institution of the combined regimen and included a fall in diastolic and lability of systolic blood pressure, postural hypotension, exertional tachycardia, fatigability, drowsiness, gastrointestinal discomfort, numbness, and tingling of the hands, and steppage gait. Laboratory studies revealed a decrease in 17-ketosteroid excretion, impaired ability to acetylate PABA, a decline in blood cholesterol and cholesterol ester levels, pro-

nounced decrease in eosinophil response to ACTH, and development of gastric hypochlorhydria. These processes were all reversible after withdrawal of the antimetabolite.

Vitamin B_6.—The evidence on vitamin B_6 deficiency in the human was reviewed at length in this section in volume 6 of the *Annual Review of Medicine* (90). Biehl & Vilter (91) have now shown that isoniazide administration is followed by an enhanced urinary excretion of vitamin B_6 and by an alteration in the ability to metabolize added tryptophan without increased excretion of xanthurenic acid. They suggest that a peripheral neuritis associated in some instances with isoniazide therapy may be due to this vitamin B_6 relationship.

The interest in vitamin B_6 as related to cardiovascular disease is heightened by the finding of unusually high values for transaminase in myocardial infarction (92). Experimental myocardial infarction produced in dogs is followed within a few hours by a similar change (93, 94). Transaminase activity of the blood can be lowered by the feeding of monkeys a diet deficient in vitamin B_6 or raised by supplementing the diet of man or monkeys with additional B_6 (95). In rats a chronic deficiency of vitamin B_6 resulted in a systolic hypertension which could be rapidly lowered by supplying the vitamin (96).

Nutrition in pregnancy.—Reports are appearing of an extensive series of investigations of the nutritional status of women during pregnancy and lactation. The most comprehensive of these reports come from Detroit (97, 98) and Nashville (99 to 106). Both investigations included dietary, biochemical, and clinical appraisals. The Detroit group studied 1064 subjects, the Nashville group 2129. These reports provide a useful background of observational data on nutrition during normal pregnancy. Both studies agree in that the nutritional levels of the subjects were not the primary factors determining health during pregnancy and the size and performance of the newborn. To this extent they set nutritional ceilings above which more abundant intakes are not to be expected to eradicate abnormalities. The Detroit studies revealed a lower nutritional level among the Negro group. The Vanderbilt analysis (103) especially focuses attention upon the effect of pregnancy and of lactation upon the nutritional state of the woman, particularly during the post partum period or whenever obstetric complication occurs. The relationship between prematurity and low caloric intake of mothers (107) is consistent with the findings from most of the recent studies. Interpretation of these relationships in terms of causation depends upon knowledge of the intake levels and of associated maternal conditions.

Historical

Perspective in science is obtained through knowledge of the history of its development and of the men responsible. A number of revealing biographies and historical appraisals of nutrition have become available. These include biographies of James Lind (108, 109), Antoine Lavoisier (110), Sir Robert McCarrison (111), and of Casimir Funk (112). The reprint (113) of Lind's

Treatise on Scurvy, accompanied by a modern summary of our knowledge of the disease, was a delightful and valuable addition to the Edinburgh Symposium (114) honoring the bicentenary of the publication of this classic work. The charming autobiography of Hopkins (115), the appraisal of his work, and excerpts from his publications must not be overlooked by one interested in nutrition.

The series of biographies appearing in the first number of each volume of the *Journal of Nutrition* now embraces 19 scientists including: Tisdall (116), Goldberger (117), Armsby (118), Holst (119), Folin (120), Hart (121), Lind (122), von Bunge (123), Rubner (124), Kellner (125), Mulder (126), Bernard (127), Beaumont (128), Magendie (129), Eijkmann (130), Lusk (131), Hopkins (132), Babcock (133), and Murlin (134).

It is hoped that this list will continue and that the present stimulating interest in the history of nutrition is setting a pattern for the future.

It is impossible adequately to summarize the past year's nutritional advances without referring to the publication of the remarkably useful three-volume reference work edited by Sebrell & Harris (135). This encyclopedic compilation is written by a distinguished group of authorities and will serve as the standard work of its sort for many years. Another valuable aid for the nutrition worker is "Standard Values in Nutrition and Metabolism" (136).

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ENDOCRINOLOGY[1,2]
(THE HORMONES)

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For its scientific basis endocrinology depends largely on hormone research. It may, therefore, be appropriate that this review should be devoted almost entirely to recent progress in this important field. The enormous output of current research, and the need for some historical perspective, has made it necessary to confine our attention to certain hormones of the pituitary, thyroid, and adrenal glands. Hypophysectomy in man will also be discussed.

The Anterior Pituitary Gland

The complex protein structures of the pituitary tropic hormones continue to elude chemical definition. In the absence of any suitable chemical methods for their routine determination in body fluids, reliance continues to be placed on biological assays which depend on the changes these hormones induce in their respective target-organs. It is not proposed to discuss the many limitations and pitfalls involved in this type of biological determination; these have recently been reviewed by Sonenberg (1) and Segaloff (2). It should, however, be remembered that great caution is needed in interpreting results obtained by these methods. The quantities of hormone involved are minute in comparison with other proteins present in the fluids under assay, and some of the end-organ effects may be of limited specificity. With these reservations in mind, an attempt will be made to review some of the recent progress in this field, in the light of earlier work.

Thyrotropin (TSH) and exophthalmos-producing substance (EPS).—In 1932 Loeb & Friedman (3) and Marine & Rosen (4) showed that hyperthyroidism with exophthalmos could be produced in guinea pigs by injecting pituitary extracts containing thyrotropic hormone (TSH). These observations were confirmed and elaborated by Smelser (5), and out of them arose the hypothesis that both the thyroid overactivity and the exophthalmos of Graves' disease might be caused by one factor, an excess of pituitary TSH. The development subsequently of a number of procedures for assaying TSH [reviewed by Albert (6)] led to many attempts to estimate this hormone in the blood and urine of patients with thyroid disorders. Whilst there was general agreement that the TSH level in normal serum was too low to be meas-

[1] The survey of literature pertaining to this review was completed in July, 1955.

[2] The authors are indebted to Mrs. R. Pitt-Rivers, F.R.S., for her helpful criticism of the section on triiodothyronine, to Drs. R. I. S. Bayliss, I. C. Gilliland and J. F. Tait for their help and criticism, and to Dr. D. Baron for assistance with the section on hypophysectomy in man.

ured by existing methods [with the possible exception of that of De Robertis (9)], high or measurable levels of this hormone were usually reported in spontaneous myxoedema, both in serum (7 to 11) [refuted by Spence (12)] and in urine (7, 13 to 15) [refuted by Cope (16)]; these tended to be highest when the myxoedema had been induced (15). In a proportion of hypothyroid cases, however, the assays were negative. In some of these there was evidence of primary hypopituitarism (9, 11); in others it seemed possible that the pituitary gland had been so affected by myxoedema as to be incapable of releasing TSH. Support for this theory was obtained by Starr *et al.* (15). These authors, though unable to detect urinary TSH in a patient with severe myxoedema of long standing, were able to do so during the early stage of treatment with thyroid extract. Later, when the basal metabolic rate had attained normal levels, the urinary TSH disappeared. These findings have been confirmed in other patients (17, 18). To explain those cases in which the assay was negative, it was also suggested that the myxoedema might be due to a selective failure of the pituitary thyrotropic function (11, 16), an explanation which now seems untenable in the light of the known failure of exogenous TSH to produce a thyroid response in cases of spontaneous or primary myxoedema, using sensitive radioiodine methods of testing (17 to 21).

In hyperthyroid patients TSH assays have produced conflicting results. Most authors have been unable to detect this hormone in the serum or urine of thyrotoxic patients without eye signs (9, 10, 11, 15, 16, 22, 23). On the other hand, in the presence of severe, progressive, or malignant exophthalmos raised levels of TSH have frequently been reported, both in the serum (8 to 10, 24) and in the urine (15). De Robertis was able to restore these levels to normal by giving thyroxine (9).

To summarize these earlier findings, it was apparent that in myxoedema, especially when therapeutically induced, there was usually a compensatory rise in TSH secretion. On the other hand, these assays provided little evidence to support the concept that thyrotoxicosis was due to excessive TSH secretion, except possibly when accompanied by severe eye involvement. It should be remembered, however, that direct comparison of the results of different authors is not feasible owing to the wide variety of TSH reference standards, and of methods of extraction and assay, which were employed. Nor is it known how much greater than normal the TSH level must be before it can be measured by these assay methods.

Interest in the role of the pituitary gland in Graves' disease has been further stimulated by recent reports of a pituitary exophthalmos-producing substance which is separable from TSH, and by new assay methods for detecting the presence of TSH in man. For some years it had been apparent that there was often a lack of parallelism between the thyrotropic and exophthalmos-producing properties of pituitary extracts. In 1946 Dobyns had noted in animals that TSH, when highly purified, tended to lose its exophthalmic effect (25). Conversely, the iodination of pituitary extracts at

pH 4.2 had been found to inactivate 95 per cent of the TSH principle whilst still leaving appreciable exophthalmic activity (26). Further work by Dobyns & Steelman led in 1953 to the separation from TSH of an exophthalmos-producing substance which they named EPS (27), and which they assayed by its effects on the intercorneal distance in the Atlantic minnow (fundulus). By this very sensitive method, originally devised by Albert (28), a response could be obtained with as little as 15 μg. of a dried EPS extract. It seemed unlikely that an inhibiting substance was responsible for these findings since EPS could be eliminated from TSH and TSH almost completely from EPS.

More recently, Dobyns & Wilson have used the fundulus method of assay to compare the exophthalmos-producing (EP) activity of serum from normal subjects and patients with progressive exophthalmos (29). Allowing for the technical difficulties involved, the preliminary results seem to favour the hypothesis that there is an excess of EP activity in the serum of patients with active or progressive exophthalmos. These findings await confirmation. Whether EPS be a single entity or a mixture of synergistic pituitary substances, as Smelser *et al.* (30) have suggested with good experimental evidence, is not known. At present there are certainly no grounds for regarding it as a hormone, nor is it easy to imagine what the normal physiological functions of such a substance might be.

Parallel with Dobyns' discoveries, Gilliland & Strudwick (31) have evolved a new and easier method for assaying TSH in the blood. Their technique is based on that of Piotrowski *et al.* (32), and, unlike some earlier methods, is unaffected by the presence of thyroid hormone in the samples being assayed. The TSH activity is determined by measuring the rate of thyroidal I^{131} discharge in newborn chicks in which the endogenous TSH secretion has been suppressed by thyroxine. Applying this method to human sera, Gilliland & Strudwick (33) have been able to detect low TSH activity in healthy subjects, and have confirmed the high levels of TSH previously reported in myxoedema. All of their nine thyrotoxic patients with severe eye signs showed a raised serum TSH, comparable with the levels in the myxoedematous patients. However, the sera of three out of the five thyrotoxic patients without severe eye signs, and of all three of the euthyroid patients with severe eye signs of Graves' disease, gave no response. Whilst these and some of the earlier results could be interpreted as evidence of pituitary overactivity in exophthalmic Graves' disease, they do not support the theory that TSH per se is the cause of exophthalmos, because equal or even greater amounts of TSH were found in the myxoedematous patients, with no eye signs, and none was detected in the exophthalmic patients who were euthyroid. It would seem, therefore, that some other factor, such as Dobyns' EPS, may be concerned in this process.

Whatever may prove to be the ultimate nature of EPS, some recent work has suggested a mechanism which might give rise to exophthalmos. In 1950 Ludwig reported that experimental exophthalmos in the guinea pig depended on the accumulation of large amounts of intercellular ground-substance and

water in the connective tissues of the orbit (34). An important constituent of this substance was hyaluronic acid. Because these changes were similar to those occurring in localized (pretibial) myxoedema, a common mechanism was suggested (35, 36) for the two conditions, which so frequently are associated. Anterior pituitary extracts were already known to have a fat-mobilising activity in animals (37, 38). Iversen & Asboe-Hansen (39) showed that this activity was also present in thyrotropic extracts, both in normal and thyroidectomised guinea pigs, and were able to suppress it with thyroxine. As well as stimulating the thyroid gland (in the intact animals), these extracts caused the following sequence of events: (*a*) mobilisation of fat from the normal fat depots, (*b*) replacement of this fat, including that within the orbit, by a mucinous hyaluronidase-sensitive polysaccharide possessing water-binding properties, and finally (*c*) protrusion of the eye-balls.

These authors claim to have found similar biochemical lesions, of a generalised nature, in the skeletal muscles of patients with progressive exophthalmos, associated with a raised serum TSH (24). If it can be confirmed that such changes occur within the orbit in the active stages of malignant exophthalmos, here may lie an answer to the mechanism of this most puzzling condition.

Melanocyte-stimulating hormone (*MSH*).—Smith and Allen observed in 1916 that the skin of tadpoles lost its colour after hypophysectomy (40 to 43). This was the first intimation of any connection between the pituitary gland and pigmentation. Later it was shown that this pigment-active agent was present mainly in the pars intermedia of the pituitary gland (40 to 46) which led Zondek & Krohn to propose that it be called "intermedin" (47, 48). These observations, though of great interest to the biologist, seemed at first to have little clinical application. Interest in this work, however, slowly extended to the mammal and to man. Krogh in 1926 had shown that horse serum had a melanophore-stimulating activity in frogs (49), and in 1933 the same was reported for human blood (50) and urine (51). The following year Konsuloff found this activity to be abnormally high in the urine of pregnant women and proposed a test for pregnancy based on this phenomenon (52 to 54).

Meanwhile, clinical observations were pointing to a possible association between pituitary activity and pigmentary changes in man. Hypopituitarism was known to be associated with diminished, and pregnancy with increased, pigmentation, and malignant melanomata had been reported to grow more rapidly in pregnant women. With the discovery of ACTH, and later of its darkening and naevogenic effects of human skin (55, 56), it seemed possible that the pigmentation of Addison's disease might be related to excessive ACTH secretion. At about this time (1952) excessive melanophore-stimulating activity was reported in the blood of patients with this disorder (57, 58), and in commercial preparations of ACTH (57 to 59).

Recent years have seen rapid progress in this field, the result mainly of the activities of Lerner, Shizume and their team at Portland, Oregon (re-

viewed in 60). These authors have proposed the name of melanocyte-stimulating hormone (MSH) for the pituitary factor which darkens the skin, the term melanocyte having recently been adopted for the mature pigment-forming cell. Partly by a process of oxycellulose adsorption, MSH has now been isolated in reasonably pure form from hog pituitaries. Though its chemical structure has not been determined, its activity in the purest form available is as high as 1×10^7 units[3] per mgm (60). The physical factors affecting the activity of this substance have been largely defined, and the posterior lobe of the mammalian pituitary gland has been shown to contain about ten times as much MSH activity as the anterior lobe.

By injecting MSH into human volunteers, Lerner and his colleagues were able to cause darkening of the skin, an effect which began within a few hours of a single large dose (60, 63). There was a marked response in a patient with hypopituitarism, as well as in the normal subjects, but no dramatic change in three cases of vitiligo. These particular preparations, when assayed, contained only minute traces of ACTH, and the amounts used in the above experiments had no effect on circulating eosinophils or urinary 17-ketosteroid excretion. A substance with melanophore-expanding activity has now been isolated from the human pituitary gland (61).

Using isolated frog-skin as the target-organ, Shizume, Lerner & Fitzpatrick (62) have developed a quantitative bio-assay method for determining MSH in blood and urine, based on that of Friedin *et al.* (64). The test depends on changes in light reflectance of frog skin when immersed in a solution containing MSH, and appears to be specific, since substances in the blood which are known to stimulate frog melanocytes, such as adrenaline, noradrenaline, hydroxytyramine, serotonin, the ergotamines, and mesantoin, are not extracted with the MSH. By this method, it has been shown that the MSH level in normal blood averages 1.3 units per ml. (range 0.4 to 2.2 units), and that the normal 24-hr. urinary excretion of MSH averages 27.7 units (range, 7.5 to 47.5 units) (65). There are no sex differences in these values in normal subjects. In pregnancy, however, MSH levels rise steadily from the end of the second month to term, after which they return to normal within a few days. Negros, albinos, and patients with vitiligo were found to have normal levels of MSH excretion. Patients with Addison's disease showed high blood and urinary levels of MSH which could be corrected by giving cortisone, and a proportion of hypopituitary patients showed a diminished output of this substance. As the authors point out, final proof of the reliability of this test will be forthcoming only when the exact chemical nature of MSH is known, and it can be shown that urinary MSH has the same structure (55).

Other substances, such as progesterone, will darken isolated frog skin,

[3] A unit of MSH has been defined as the degree of darkening, measured with a photoelectric reflection meter, of isolated frog skin caused by .04 microgram of a lyophilised water extract of beef posterior pituitary powder (62).

though pregnanediol, in which form this steroid is excreted in the urine, is inactive by this method of assay (65). Stolte *et al.* have pointed out that there are two ways in which the hypophysectomized frog may become discoloured: either totally, as occurs after intermedin (MSH) injection, or partially, affecting only the hind parts of the body, as after injections of pregnancy urine or serum, or of pure human chorionic gonadotrophin (66). This second type of discolouration is that obtained in the Konsuloff pregnancy reaction (*supra*) and is apparently not due to MSH (67).

Corticotropin.—Since the Sayers introduced the ascorbic acid-depletion technique for the assay of ACTH (68), a number of attempts have been made to apply this very sensitive method to the measurement of ACTH in blood (69 to 76) and urine (77). Apart from the hazards of extraction, which are common to all pituitary tropic hormone assays, a further difficulty with ACTH has been the great instability of this hormone in the presence of blood. Using methods which were mostly based on rapid extraction of plasma with acid acetone, some authors reported positive assays in normal human blood (69, 72) [refuted by Taylor *et al.* (70)], in blood from patients with Addison's disease (70, 76), and from adrenalectomised rats (73, 74). One group of workers also obtained high levels of plasma ACTH in Cushing's syndrome and in patients under surgical or cardiological stress (71).

In the light of recent work by Sydnor & Sayers, some of the positive results obtained by other methods should be interpreted with great caution (78) more especially on account of the high levels of ACTH reported in the plasma (69, 71, 72, 76). Sydnor & Sayers (79), using acetic acid extracts of blood, from which ACTH is then adsorbed by Astwood's oxycellulose technique, have obtained good recoveries and consistent results which are of great physiological interest. These authors have found that the plasma ACTH of nonstressed rats is too low for detection by this method; the concentration, therefore, is believed to be less than 0.5 milliunit (mu.) per 100 ml. (80). It is calculated that the biological half-life of ACTH in the rat is between 0.95 and 1.25 min. (81), and the pituitary content of ACTH about 70 mu. (80). Within one to two weeks of adrenalectomy, the blood titre has risen to 2 to 4 mu. per 100 ml. and the pituitary content to 170 mu. (80). After stress, the blood titre now rises further, to about 10 to 15 mu. per 100 ml. (82). Having first established that the presence of cortisol (hydrocortisone) does not interfere with the quantitative recovery of ACTH in vitro, Sydnor has shown that pituitary release of ACTH in the adrenalectomised rat can be inhibited by giving cortisol intravenously 1 to 2 min. before applying a stressful stimulus (82).

Applied to man, the Sydnor assay has shown significant ACTH titres in the plasma of patients with Addison's disease (83) and with untreated adrenogenital syndrome (84). Adults, afebrile children, and cortisone-treated cases of adrenogenital syndrome gave negative assays (83), suggesting, as in the normal rat, that the levels were less than 0.5 mu. per 100 ml. Kelley,

however, has reported raised levels in children with active and inactive rheumatic fever, though not in the early stages of the disease (85).

Other workers have tried to estimate the urinary excretion of ACTH by direct injection of urine into hypophysectomized rats (77). By this method it is claimed that normal urine contains between less than one and eight international units of ACTH per litre (77). Though high ACTH titres were found in a case of active Cushing's syndrome (77), much more evidence is needed in order to settle the vexed question of whether this syndrome is secondary to pituitary overactivity (*infra*), the present position being analogous in many ways with that of Graves' disease.

The Adrenal Cortex

It is in the understanding of the adrenal cortex, more than in any other branch of endocrinology, that the most spectacular progress has been made in recent years. For this much credit is due to the pioneering work of Zaffaroni *et al.* (86, 87) and Bush (88) in applying the methods of paper chromatography to the separation and estimation of adrenocortical steroids in body fluids, and of Pincus and his associates at the Worcester Foundation in elucidating some of the mechanisms of steroid biosynthesis within the adrenal cortex.

The secretion of the adrenal cortex.—Recent work on the composition of the adrenocortical secretion in man and other mammalian species has been reviewed by Bush (89) and need only be summarised here. Direct measurements on adrenal venous blood have provided sound evidence for the secretion of cortisol (hydrocortisone), corticosterone (compound B), 11-β-hydroxyandrosterone, and aldosterone. The evidence that cortisol and aldosterone are probably the predominant adrenocortical hormones in man will be discussed later in the section on aldosterone.

The adrenal androgens present a more difficult problem because there is no satisfactory bioassay method for their detection in blood that will allow comparison with chemical studies (89). Although it is still uncertain whether most of the adrenal androgen secretion has been chemically accounted for, three 17-ketosteroids have been partially identified in mammalian adrenal venous blood (90, 91), including 11-OH-androstenedione in man (92). There is also evidence that the adrenocortical secretion contains androgenic activity (93). To quote Bush (89):

> It may be objected that the chemical approach to the secretion of the adrenal cortex has not told us much that we did not know or suspect beforehand, but this objection neglects the principal aim of endocrinology which is the accurate description of the functions of the endocrine glands in terms of chemically defined hormones. The chemical study of endocrine secretions plays a modest but essential role in endocrinology, if only by setting limits to speculation.

Genesis of the adrenocortical secretion.—The genesis and subsequent metabolism of the adrenocortical steroids have been reviewed by Dorfman &

Ungar (94) and by Hechter & Pincus (95). Theories as to the pathways of steroid synthesis and their derangement in certain diseases of the adrenal gland, which have arisen from this work, have been further elaborated by Dorfman (96, 97). These hypotheses provide an essential basis for the interpretation of many aspects of adrenocortical function.

Current concepts of steroidogenesis assume, with much sound evidence, that both cholesterol and acetate are the natural precursors of the adrenocortical steroids. From this point onwards there are two parallel lines of synthesis, the first beginning with the conversion of cholesterol to pregnenolone, the parent compound of the C_{21} steroids, and the second with the conversion of either cholesterol or acetate (98) to dehydroisoandrosterone (DHA), from which certain C_{19} androgens stem. The second stage, along both lines, is the conversion of these key compounds, pregnenolone to progesterone and DHA to androstenediol (androsterone). This stage is dependent on the enzyme, 3 β-dehydrogenase, which oxidises the Δ^5-3 β OH group to a Δ^4-3 ketone group. Further progression, in the C_{21} series, depends on hydroxylation of progesterone, by the appropriate enzymes, and proceeds along divergent lines, the first via 17-OH-progesterone to the 11,17,21-OH compound, cortisol, the second via 21-OH-progesterone (deoxycorticosterone) to the 11,21-OH compound, corticosterone.

In the C_{19} (androgen) series only 11 β-hydroxylase is important, converting androsterone to its 11 β OH analogue, which then provides a variety of 11-oxygenated-17-ketosteroids. According to Hechter & Pincus, the C_{19} steroids are unlikely to be major precursors of corticosteroids, since no recognisable C_{21} steroids are found after infusing a variety of C_{19} steroids through the isolated bovine adrenal. Nevertheless, the possibility remains that, under certain conditions, C_{19} steroids may accept C_2 fragments to form C_{21} steroids (99). Aldosterone, a C_{21} compound, has not yet been incorporated into the postulated reactions of corticosteroid biosynthesis.

An important assumption in applying the above scheme to clinical problems is that ACTH does not stimulate steroidogenesis beyond the formation of pregnenolone and DHA. What the adrenal gland then produces depends on the relative proportions of the hydroxylating enzymes which it contains. There is much experimental evidence in support of this view, derived mainly from studies *in vitro* and on isolated adrenal glands (100, 101). That the action of ACTH is merely quantitative is in accord with physiological studies in hypophysectomised animals; these lack many of the symptoms of adrenocortical insufficiency, such as occur after adrenalectomy, and continue to secrete corticosteroids, albeit at a low level (102). According to Hechter (99, 103), the specificity of ACTH in corticosteroid biosynthesis would appear to reside not in its control of a specific tissue enzyme peculiar to the adrenal gland (similar enzymes probably participate in the production of pregnenolone from cholesterol in the ovary following stimulation by luteotropic hormone), but in its specific affinity for adrenocortical tissue.

This summary of recent views on steroid synthesis is best concluded by the cautious words of Hechter & Pincus (95):

> The postulated scheme of corticosteroidogenesis . . . as it now stands (1954), represents a series of deductions, based primarily on the ability of substrates to react. While this is a useful method to initiate the study of metabolic pathways, there are innumerable examples of *in vitro* reactions which are known to be of minor importance under physiological conditions.

So far as is known, cortisol is the only physiologically significant (i.e., naturally occurring) suppressor of pituitary ACTH secretion in man. Thus, adrenal androgen production, via DHA, must also depend on the circulating level of cortisol. This has important implications when one comes to consider the mechanism postulated for the adrenogenital syndrome. In this condition the available evidence strongly suggests that there is a metabolic block in the production of cortisol. The result, therefore, is an accumulation of 17-OH progesterone and earlier intermediates within the adrenal gland, and an increased urinary excretion of their metabolites, pregnanediol and pregnanetriol (96, 104 to 106). As a result of examining the individual steroid patterns in these cases, Dorfman believes that the block can be located specifically at the 21-OH step, since C_{17} and C_{11} hydroxylations are not affected as shown by the raised urinary excretion of 17-OH-pregnanolone and 11 β-OH-androsterone (96). The deficiency which Dorfman postulates is believed to be of various degrees, and to lead to a relative lack, not only of cortisol, but also of the other 21-OH compounds, corticosterone, deoxycorticosterone, and possibly also of aldosterone, if this last hormone can be shown to arise directly from progesterone. Marked lack of these steroids would explain the symptoms of adrenal insufficiency which have been reported in a proportion of these cases, such as hypoglycaemia (109, 110) and sodium depletion (111).

As a logical sequence of cortisol deficiency, there is an increase in ACTH secretion, causing excessive production of adrenal androgens and of the cortisol precursors that have already been mentioned. It must be remembered, however, that the virilising features of this disease have not yet been adequately accounted for on a basis of known androgenic activity of the steroids which are being formed; nor is it known whether 17-OH-progesterone is converted into other steroids with androgenic activity (105).

The above explanation of the adrenogenital syndrome accords well with other findings, such as the now well-established suppression of the symptoms and abnormal biochemistry of this disease by exogenous cortisone or cortisol (113 to 117). Moreover, high levels of ACTH, which can be suppressed by cortisone, have been reported in the blood of these cases (83), and, although the plasma 17-hydroxycorticoid levels are often normal, they do not rise significantly after ACTH infusion as they do in normal subjects (106, 118 to 121), suggesting that the adrenal glands are already under maximal stimulation.

Dorfman has also applied his scheme of steroid synthesis to Cushing's syndrome and to cancer of the adrenal glands (96). When Cushing's syndrome is due to adrenocortical hyperplasia, it is suggested that the primary disorder is one of increased ACTH secretion which causes a relatively greater production of pregnenolone, and hence of glucocorticoids, than of DHA. If this be the case, however, it must also be assumed that the pituitary gland has lost its sensitivity to the inhibiting effects of cortisol. Moreover, it is hard to account on this basis for the presence of Crooke's cells in the anterior pituitary gland. There is some evidence that Crooke's changes may be secondary, rather than primary, to excessive glucocorticoid production, since they can be induced both in animals (122) and in man (123) by giving large doses of cortisone. The elevated urinary excretion of C_{19} derivatives in Cushing's syndrome could be due to metabolites of C_{21} steroids, such as are known to be produced from cortisone and cortisol (124 to 126).

In adrenal carcinoma, Dorfman (96) assumes that the adrenal glands have achieved a certain degree of autonomy, and that the level of ACTH secretion is then of little consequence. This would accord with the relative inability of exogenous ACTH or cortisone to affect the clinical or biochemical pattern in this disease. The secretion of both C_{19} and C_{21} steroids is increased, usually with a predominance of the former compounds. Thus the production of DHA and its Δ_5 and Δ_1 derivatives may be enormous.

Tests of adrenocortical function and their application.—(*a*) *17-hydroxycorticosteroids in blood and urine:* The application of the Porter-Silber colour reaction (127) to the measurement of 17-hydroxycorticoids in blood (128 to 130) and urine (131) has given a great impetus to the study of adrenal glucocorticoid activity, and represents an important advance over previous methods of assessing this function in man. In the blood method, devised by Nelson & Samuels (128, 129), the extracted steroids are estimated by the Porter-Silber reaction which is relatively specific for 17,21-dihydroxy-20-ketosteroids, and, therefore, does not measure corticosterone. However, since cortisol and its metabolite, tetrahydrocortisone (130), are the principal 17-hydroxycorticoids in human blood (*supra*) and corticosterone is present only in very small quantities, this method, under most conditions, provides an adequate index of glucocorticoid concentration. As both Nelson (133) and Bayliss (132) have pointed out, there are certain limitations to the use of this method as an indéx of adrenocortical activity, the plasma steroid concentration being the resultant of several factors besides the rate of secretion, such as metabolism in the liver and peripheral tissues, and excretion in the urine and faeces.

Some of the factors which are known to influence the plasma concentration of 17-hydroxycorticoids have been discussed recently by Bayliss (132). Though the normal level of these substances in the plasma may vary widely, e.g. 95 per cent range of 3 to 26 μg. per 100 ml. in one series (134), the mean levels reported by different authors have ranged between 9 and 14 μg. per

100 ml. (134 to 140).[4] Except in newborn infants (*infra*), there are no significant differences in these values due to age or sex. There is a pronounced diurnal variation in these levels, which are lowest at midnight and highest at about 6 a.m. Emotional factors, such as excitement and apprehension, will cause them to rise, though seldom above 20 μg. per 100 ml. (132). Caution is therefore required in assessing the significance of the normal range. During pregnancy there is a progressive rise in plasma 17-hydroxycorticoid concentrations [to about 24 μg. per 100 ml. during the last month in one series (143)], with a return to normal levels within a few days of delivery (142 to 144). Some of this increase is possibly of placental origin, and normal plasma 17-hydroxycorticoid levels have been reported in a pregnant patient with Addison's disease (121). These findings are of great interest in view of the well-known amelioration of rheumatoid arthritis by pregnancy. Salicylates in therapeutic doses have not been found to increase the plasma 17-hydroxycorticoids (146), despite earlier suggestions that they stimulated adrenocortical activity (147).

The most potent physiological stimulus to the adrenal cortex, as measured by the plasma 17-hydroxycorticoids, is intravenous infusion of ACTH. The magnitude of the adrenal response depends on the amount of ACTH infused (137) and on the duration of the infusion (148). Thus, whereas a single intravenous injection of 20 units of ACTH may provoke only a small and transient adrenal response, maximal stimulation is usually obtained, after a few hours, by infusing this hormone at a rate of 1 unit an hour, and there is some response at 0.25 unit an hour (137). Other authors prefer to give ACTH as a single intravenous injection and have reported a brisk response after as little as 0.1 unit of the hormone (149). The intravenous infusion of epinephrine has no significant effect on the level of plasma 17-hydroxycorticoids (150).

Low or insignificant levels of plasma 17-hydroxycorticoids have been reported in newborn infants (140), in Addison's disease (121, 132, 134, 151), and in severe hypopituitarism (121, 132), although the level may be normal in incomplete cases of the last condition (132). In the adrenogenital syndrome the levels are normal or reduced, and in Cushing's syndrome, whether this be due to adrenal hyperplasia, adenoma, or carcinoma, they are high (121, 132). Levels in the range encountered in Cushing's syndrome are also found after exposure to heavy stresses such as surgical operation (152, 163), or myocardial infarction (132), and in severe terminal illness (132, 151). Acute infections are accompanied by a moderate increase of plasma 17-hydroxycorticoids, although low levels, which respond normally to ACTH, have been reported in the subacute and chronic stages of rheumatic fever (138). However, as Nelson (133) and Bayliss (132) have pointed out, high val-

[4] Direct measurements of cortisol in normal subjects give a mean concentration of about 3 μg. per 100 ml. whole blood (141).

ues do not necessarily imply that the adrenocortical secretion is increased; in some cases they may be due to diminished tissue utilisation of hormone, impaired hepatic function, or renal failure.

One of the many difficulties in attempting to assess adrenocortical function by a single blood estimation is the profound variation which may occur in adrenal activity from hour to hour. To overcome this limitation, and so make it possible to assess adrenal activity over a given period of time, Reddy, Jenkins & Thorn (131), and Glenn, Nelson *et al.* (153, 154), have applied the Porter-Silber colour reaction to measurement of the urinary 17-hydroxycorticoids. Thorn *et al.*, using this technique, did not find that there was any increase in urinary 17-hydroxycorticoid excretion after physical or mental exertion, exposure to cold, or anoxia, although emotional factors and surgical operations provoked a marked adrenal response (155). In normal subjects, the urinary output of these steroids is higher by day than by night, the diurnal rise sometimes beginning at 3 a.m. (156). This fundamental rhythm has not been altered by forced inactivity in bed, night work, starvation, or 4-hourly feeds, but has been reversed by nocturnal administration of ACTH (156). Infusion of epinephrine does not increase the urinary output of 17-hydroxycorticoids, even though it causes a marked fall in the blood eosinophils (155).

Di Raimondo *et al.* (157) have studied the effects of ACTH infusion on the hourly urinary excretion of 17-hydroxycorticoids. From their data on the minimal effective doses needed to cause an adrenal response, these authors have estimated that the daily basal output of ACTH by the human pituitary gland is probably less than 1 USP unit. They have also found a diurnal variation in the response to ACTH, which runs parallel to the spontaneous diurnal variation in adrenocortical activity, suggesting that this last rhythm is not under the control of endogenous ACTH secretion.

Norymberski (158) has devised an alternative chemical method for measuring the urinary 17-hydroxycorticoids which depends on converting the so-called 17-ketogenic steroids (which include cortisol, cortisone, and some of their metabolites, but not corticosterone and its derivatives) into 17-ketosteroids. Whilst it is early as yet to assess the value of this method, a reasonably good agreement between it and the method of Reddy, Jenkins & Thorn (131) has been found in at least one laboratory (159).

(*b*) *The adrenal response to ACTH and cortisone in endocrine disorders:* Since 1948 the response of the adrenal cortex to stimulation by exogenous ACTH has been recognised as one of the more specific and quantitative tests of adrenal function (148, 160, 161). The recent development of chemical methods for estimating 17-hydroxycorticoids in blood and urine (*supra*) has provided a more direct means of assessing this response, and recent studies have confirmed the clinical value of this test (119, 121, 137, 149, 155, 162, 163).

In disease states, such as primary adrenal insufficiency and hypopituitarism, measurements of the plasma 17-hydroxycorticoids before and after

ACTH infusion give a more precise estimate of adrenocortical capacity than any single estimation. Only occasionally does ACTH produce any response in Addison's disease (164), even when there are significant resting levels of plasma or urinary 17-hydroxycorticoids (132, 165). Since some of these patients show clinical evidence of residual adrenocortical function, it is tempting to assume that any adrenal remnants that may persist are already under maximal stimulation from endogenous ACTH, and so unable to respond further to exogenous hormone (132). In hypopituitarism there is usually a subnormal response to ACTH (121, 132), and the degree of failure of response may be related to the duration of adrenal atrophy (132). In the adrenogenital syndrome, the poor response of the plasma 17-hydroxycorticoids to ACTH (105, 119 to 121, 137, 164, 166) has provided further indirect evidence of a block in the adrenal synthesis of cortisol (*supra*). Except in this syndrome and adrenal carcinoma, the response to ACTH appears to be partly related to the degree of adrenocortical hypertrophy at the time of the test (132). Thus, exaggerated responses have been reported during the third trimester of pregnancy (121) and are usual in Cushing's syndrome due to bilateral adrenal hyperplasia (121, 132). This test, therefore, is useful in distinguishing the last condition from adrenal carcinoma in which there is no response to ACTH (121, 167). Variable findings have been reported in patients with adrenal adenomas, the sensitivity to ACTH probably depending on the degree of autonomy of the tumour (121, 167).

An alternative test for distinguishing between adrenal carcinoma and hyperplasia is based on the response of the adrenal cortex to the suppression of endogenous ACTH secretion by cortisone. When given in large doses, this steroid causes a marked fall in the urinary 17-ketosteroid excretion in those cases of adrenal virilism, and, to a lesser extent, of Cushing's syndrome attributable to adrenal hyperplasia, but not in those cases caused by adrenal carcinoma (168 to 170). Other authors have shortened the duration of this test by giving an intravenous infusion of hydrocortisone over 4 hr. instead of intramuscular cortisone injections over several days (171).

(*c*) *The neutral 17-ketosteroids in urine and blood:* The urinary neutral 17-ketosteroids form a motley group of metabolic end-products, derived almost entirely from adrenal and testicular sources (172). In the healthy male about one-third of them is testicular, and about two-thirds adrenocortical, in ultimate origin. Quantitatively the urinary 17-ketosteroids are now regarded as an incomplete index of adrenocortical activity. They do not, for example, reflect the excessive glucocorticoid production in Cushing's syndrome caused by adrenal hyperplasia. However, in adrenal virilism there is a rough accordance between the virilising symptoms and the high 17-ketosteroid output.

The development of chromatographic-colorimetric techniques for fractionating the urinary neutral 17-ketosteroids has provided a more qualitative, though still limited, index of adrenocortical activity. In 1946 Dingemanse *et al.* (173), using alumina columns and the Zimmerman reaction, were

able to separate seven, and later eight (I-VIII) (124), major 17-ketosteroid fractions in normal urine. Of these, II and III (β-fractions) consisted mainly of the β-17-ketosteroids, isoandrosterone, and dehydroisoandrosterone (DHA); IV was androsterone, V was etiocholanolone, and VI and VII were 11-oxy-17-ketosteroids. Of these compounds, androsterone, isoandrosterone, and etiocholanolone (the first two are weakly androgenic) are known to be derived from both testicular (testosterone) and adrenal (DHA) sources (172). DHA, also a weak androgen, is entirely of adrenal origin (172).

Dingemanse's techniques have been further developed and applied on a microscale by a number of workers (174 to 181), and have provided much data from which certain conclusions can now be drawn. In healthy adults of either sex DHA forms a relatively constant, though occasionally negligible (98), proportion, usually 15 to 26 per cent, of the total 17-ketosteroid output (98, 182 to 184).

The lack of appreciable sex-differences in the chromatographic fractions, or of any specific pattern in male hypogonadism, supports the view that the 17-ketosteroids consist largely of metabolic waste-products of limited physiological significance. Nevertheless, abnormal chromatographic patterns have been reported fairly consistently in certain adrenal disorders and may be of clinical significance. Thus, in adrenal carcinoma, and sometimes in virilism due to adrenal hyperplasia, there tends to be a great preponderance of DHA, and the androsterone/etiocholanolone ratio is often raised (124, 179). In Cushing's syndrome without adrenal tumour there tends to be a normal DHA proportion, and the androsterone/etiocholanolone ratio is low; the 11-oxy-17-ketosteroids are increased, due probably to excessive cortisol secretion (179, 185). An excess of urinary DHA can also be detected by colour reactions, such as that of Allen (186), which remain useful as screening tests for the presence of adrenal tumours.

It is well known that in normal subjects ACTH increases 17-ketosteroid excretion, whereas cortisone and cortisol diminish it (160, 187). It has been shown by chromatographic analysis that this effect of ACTH is mainly attributable to increased outputs of 11-oxy-17-ketosteroids, of etiocholanolone, and, to a lesser extent, of DHA (185, 188, 189), and that these changes vary widely in magnitude and relative proportions regardless of age (189, 190). With cortisone the effects are more consistent; all fractions are usually depressed, excepting the 11-oxy-17-ketosteroids (187, 190, 191). Similarly, when cortisone is given to totally adrenalectomised ovariectomised patients, there is a resumption of 17-ketosteroid excretion, now composed almost entirely of 11-oxy-17-ketosteroids, mainly 11-keto- and 11-hydroxy-etiocholanolone (192).

The total 17-ketosteroid excretion is usually normal in idiopathic hirsutism (193, 194) and in the Stein-Leventhal syndrome (195, 196). The search for possible chromatographic abnormalities in these two conditions has been largely unsuccessful (194, 196), though an excessive proportion of DHA has been reported in a few cases of idiopathic hirsutism (193, 194) and of the

Stein-Leventhal syndrome (195, 196). The first of these disorders is usually believed to be of constitutional origin (194). In the second, however, as also in arrhenoblastoma and certain other rare masculinising tumours of the ovary, the nature of the presumed virilising agents remains a mystery; it has been suggested that they may be ovarian androgens which are metabolised along pathways independent of the 17-ketosteroids (196).

Cortisone has been shown to depress DHA excretion in a few patients with adrenal hyperplasia and idiopathic hirsutism whether or not the 17-ketosteroid excretion is high (191, 197, 198). Cortisone also produces this effect in healthy persons; in a case of hirsutism such evidence cannot therefore be used to support an adrenal aetiology.

Interest in DHA as an index of adrenal activity has been further stimulated by recent reports of the isolation and measurement, by chromatographic techniques, of this steroid in human plasma (182, 199, 200). Migeon & Plager (200) found that the mean level of DHA in normal male plasma was 40.5 μg. per 100 ml. In normal females the level varied to some extent with the phase of the menstrual cycle but was essentially no different from that of the males. In prepubescent children the levels were low. Migeon has already reported a rise in plasma DHA after ACTH, and in congenital adrenal hyperplasia and some cases of Cushing's syndrome (201). The results of further application of this technique to the study of adrenal disorders will be awaited with interest.

In conclusion, there now seems to be little doubt that the level of DHA in both blood and urine is related to adrenocortical activity (98), and that testosterone is not a precursor of DHA (202). The physiological and pathological significance of this weak androgen may become clearer when more is known about its precursors within the adrenal cortex (98).

Aldosterone.—There have been a number of reviews during the past year dealing with recent advances in the adrenocortical field, and particularly with the new hormone, aldosterone. The isolation and elucidation of the structure of this compound have been described by Wettstein (203),[5] whereas the more biological aspects have been emphasised in an excellent general review by Gaunt *et al.* (205). It is not the present intention to duplicate these reviews but rather to consider the possible influence of the discovery of this very potent salt-retaining hormone on future outlook in clinical endocrinology.

The secretion of aldosterone.—From 1928, when extracts of the adrenal gland capable of maintaining the life of adrenalectomized animals were first prepared, one or another of the physiological actions of the potent hormones have been emphasised in turn. In the course of these studies a number of theories as to the nature of adrenocortical secretion have been put forward in an attempt to explain the metabolic disturbances developing after adrenal-

[5] The structure has been confirmed by total synthesis of the hormone as a racemic mixture according to recent preliminary reports (204).

ectomy or as a result of adrenal dysfunction. These may be classified into three types:[6] (*a*) The multihormone concept of Selye, Kendall and others envisaged the secretion of a number of hormones which individually had an almost specific action on either mineral or carbohydrate metabolism. (*b*) The unitarian concept (206) which regarded the secretion of the adrenal cortex as fixed in composition, but varying in rate, and comprising either several different steroids produced in a constant ratio, or, more likely, a single hormone which could account for all the metabolic activities of the gland. (*c*) The more complex concept, which in the light of existing knowledge seems most likely to be correct, considers that a number of hormones are secreted by the adrenal cortex which all have some effect on both mineral and carbodydrate metabolism, and that the ratio in which these hormones are secreted may vary under different physiological and pathological conditions.

The multihormone concept arose from studies on the potencies of the available crystalline compounds and purified adrenal extracts in various bioassay procedures. In these experiments it was found that, whereas compounds such as cortisol (hydrocortisone) and cortisone had a great effect on carbohydrate metabolism, they had little or no activity in the life survival or the muscle fatigue tests, which were thought to be primarily concerned with the effects of steroids on the salt metabolism of adrenalectomised animals. Deoxycorticosterone, which was readily available for experimental studies, had little effect on liver glycogen deposition and other aspects of carbohydrate metabolism, although it was potent in its effect on mineral metabolism. The amorphous fraction was thought to be qualitatively similar to deoxycorticosterone. Corticosterone was recognised as having an action on both types of metabolism, but few investigators had the opportunity to study this compound. Adrenal steroids, therefore, tended to be classified into salt- and sugar- active hormones or mineralo- and glucocorticoids.

More recently, the therapeutic use of cortisone and cortisol (207) has enabled the metabolic effects of these hormones to be studied in man. It soon became apparent that the three most active of the known glucocorticoids, cortisol, cortisone, and corticosterone, could all produce sodium retention both in intact and adrenalectomised subjects (208 to 210). Since the administration of cortisone (211) and cortisol (212) could reproduce the observed effects of ACTH in human subjects, many people considered it unnecessary to postulate the existence of specific hormones, at least for the control of mineral and carbohydrate metabolism. In addition, the work of Verzar and his group (213 to 215), showing that deoxycorticosterone had an action on carbodydrate metabolism, raised considerable doubt as to the validity of dividing adrenal steroids into mineralo- and glucocorticoids

[6] The androgenic secretion of the gland and hence Albright's theories will not be considered here.

Consequently the unitarian theory gained wide acceptance, more particularly as evidence from the direct chemical analysis of adrenal venous and peripheral blood became available.

Perfusate studies, both *in vivo* (216, 217) and in the isolated gland (218), showed clearly that cortisol and corticosterone, or both, were the major active end-products of corticosteroid biosynthesis. The work of Bush (219, 220) also demonstrated that, although the ratio of these two compounds varied in different species, the relative proportion in which they were secreted remained unaltered under different physiological conditions, or in response to stimulation by ACTH. In man both cortisol and corticosterone have been isolated from adrenal venous blood (221 to 223), and cortisol has been shown to be the major, if not the only, active adrenal steroid in peripheral blood (128, 137, 223 to 225). Failure to detect the only known highly active mineralocorticoid, deoxycorticosterone, in physiologically significant amounts, seemed to many to provide conclusive evidence in favour of the unitarian concept.

The first indication that the human adrenal cortex might secrete a sodium-retaining hormone other than deoxycorticosterone (DOC) came from the work of Luetscher and his team at Stanford (226). Using a bioassay procedure, they were able to demonstrate in the urine of certain oedematous patients a substance, believed to be of adrenal origin, with biological properties similar to DOC. Its chromatographic behaviour differed from that of DOC, suggesting a more highly oxygenated compound (227). Several other groups of workers (228 to 230) also detected sodium-retaining material in the urine of a number of pathological cases.

Parallel studies by Tait, Simpson & Grundy, using a highly sensitive bioassay (231) and the paper chromatographic methods developed by Zaffaroni & Burton (86) and Bush (88), established the existence in adrenal gland extract of a hitherto unidentified compound with greater electrolite activity than that of any of the known active steroids (232 to 234). This substance, provisionally named electrocortin, closely resembled cortisone and cortisol in the chromatographic behaviour of the free compound, but differed from them in the formation of a diacetate on acetylation. A compound with these properties was also detected in the adrenal venous blood of the dog (235, 236) and in the adrenal perfusate of the monkey (235), thus providing good evidence for its secretion by the mammalian adrenal cortex. Following the isolation of this compound in crystalline form (237, 238), and the elucidation of its chemical structure (239), it became possible to establish the identity of the sodium-retaining material isolated from the urine of nephrotic subjects (240) and from the adrenal venous blood of the dog (241) with the compound, now renamed aldosterone, isolated from adrenal gland extract. Although the isolation of aldosterone from human adrenal venous blood has not been reported, there is good evidence for its presence in normal human peripheral blood (242). The absence of detectable activity in the urine of

Addisonian and bilaterally adrenalectomised patients (243, 244) leaves little reason to doubt that aldosterone, as well as cortisol and corticosterone, is secreted by the human adrenal cortex.

It has now been established with certainty that the ratio of cortisol and its metabolites to aldosterone in human blood and urine can be altered considerably from normal under certain conditions to be described later. Although these variations could be explained by differential changes in inactivation or renal clearance, more direct evidence based on analysis of the adrenal effluent blood of animals indicates, at least in many of these conditions, that the ratio of secreted compounds is involved. Kass *et al.* (245) have also shown that chronic administration of ACTH to rabbits can even alter the secreted ratio of corticosterone and cortisol.

Clinical studies, using therapeutic amounts of cortisone and cortisol, and the studies of Pitts & Roberts (246) and of Garrod *et al.* (247) in the dog, have established that the so-called glucocorticoids can produce sodium retention. Simpson & Tait have also shown that all of the known active adrenal steroids present in gland extracts will affect the urinary Na/K ratio of adrenalectomised rats in a unidirectional manner under the conditions of their test (231). Whereas the possible potency of deoxycorticosterone in the liver glycogen deposition test is still controversial, the demonstration that aldosterone is one-third as active as cortisone in this assay (248) has established that all the adrenocortical hormones of known physiological significance have some action on both carbohydrate and mineral metabolism.

From these considerations it would appear that the recent more complex interpretation of the nature of adrenocortical secretion is most likely to be correct. It therefore follows that no single test of adrenocortical function, be it estimation of 17-ketosteroids for androgenic, 17-hydroxysteroids for glucocorticoid, or aldosterone and other possibly related compounds for sodium-retaining activity, can provide information as to the state of adrenal function as a whole; only under certain circumstances will all, or even any two, of these metabolic activities be correlated. Moreover, although classification into these functions may sometimes be convenient, considerable overlapping may occur, e.g. the glucocorticoid secretion may contribute to both androgenic and sodium-retaining activity of the gland; and it is still uncertain whether all the active hormones have yet been isolated.

Aldosterone in biological fluids.—The high potency of aldosterone in those assays designed to measure mineralocorticoid activity of adrenal steroids has so far provided the most common method for the estimation of this hormone in clinical studies. In many cases fractionation of the material has preceded assay. However, even in crude extracts, it is often assumed that aldosterone is the only compound present with such activity.

There is as yet no conclusive evidence that aldosterone can account for all the sodium-retaining activity of crude whole adrenal extract (249), and it is possible that other compounds, at present unidentified, will be isolated from this source (250). Reports from the Worcester Foundation (251) suggest that one such compound, clearly not aldosterone, has been detected

following the perfusion of progesterone though the cow adrenal. Since the original isolation studies (252), much doubt has been expressed as to whether deoxycorticosterone is in fact a natural product of the adrenal cortex. Later workers, using mild fractionation procedures, have, however, confirmed its presence in adrenal extracts (86, 253), and have detected small quantities in perfusates of the isolated gland (218). Farrell *et al.* (254), have now shown that deoxycorticosterone is released into the adrenal venous blood of the dog, though probably not in amounts which are physiologically significant, and that the level is reduced after hypophysectomy and increased after ACTH administration. Although, therefore, it is probably not a physiologically important constituent of normal secretion, increased production of deoxycorticosterone may occur under conditions of abnormal steroidogenesis. Finally, as already emphasised, under certain conditions cortisol and corticosterone may contribute significantly to the electrolyte activity of such extracts. A detailed study on adrenal venous blood of the dog has shown that 40 per cent of such activity could be accounted for by the cortisol and corticosterone present, even when measured by the Na/K bioassay, which tends to exaggerate the relative potency of aldosterone (235). Moreover, Bush (255) has reported that, under abnormal conditions, the ratio of cortisol to corticosterone secreted may alter significantly in favour of the more mineral active corticosterone. Changes in the composition of adrenal secretion have also been reported by Venning *et al.* (256) in a patient with Cushing's syndrome. Prior to subtotal bilateral adrenalectomy only small amounts of sodium-retaining activity could be detected in the urine. One month after operation functional adrenal tissue was found to be present. The urine then showed greatly increased levels of such activity. Fractionation of the extract on paper indicated the presence of aldosterone and a second, less polar, active compound which has not yet been identified. It should be borne in mind, however, that the existence of such unidentified active compounds has not yet been confirmed and that there is considerable risk of contamination with aldosterone of separated material obtained by such methods. Further information on these findings is, therefore, awaited with great interest.

The detection and estimation of aldosterone.—The major metabolites of cortisol in urine would appear to be tetrahydrocortisol and tetrahydrocortisone as glucuronides. The corresponding metabolites of aldosterone have not yet been isolated, and studies involving the analysis in blood or urine have, therefore, been confined to the estimation of the $\Delta_4\alpha\beta$ unsaturated ketone itself. About 0.5 μg. of this compound can be extracted at neutral pH from a 24 hr. specimen of normal urine (272). It is still not certain whether further amounts of the free compound can be liberated by enzymatic hydrolysis (243, 257 to 261), but much greater amounts of the compound can be extracted after acidification of the urine to pH 1 for 24 hr. (258). No quantitative method for the estimation of the free compound in human urine or blood has as yet been published, although certain preliminary work has been undertaken (86, 88, 234, 241, 257, 267 to 272).

The free compound is usually estimated by bioassay, and a number of

suitable methods have now been published (230, 236, 243, 262 to 265). The most sensitive, but not necessarily the most accurate, appear to be the Na/K ratio test (231) and the intravenous assay in adrenalectomised rats (266). However, two important sources of error in such determinations must not be overlooked: (*a*) Nonpecific reduction of sodium excretion may occur as a result of a toxic action of extract or solvent; (*b*) The presence of appreciable quantities of cortisol and cortisone may, under certain circumstances, obscure the action of aldosterone. This is particularly true of those assays in which cortisol and cortisone promote sodium excretion (230, 263 to 265). No such interference has been observed in those assays employing low sodium and water loads (231, 260).

It is obvious, with the extremely small quantities of aldosterone present in urine and blood, that its determination still constitutes a research problem and, therefore, that values quoted in clinical studies will deserve critical examination for some time.

Aldosterone in normal and pathological states.—Aldosterone has been detected with reasonable certainty in the peripheral blood (242) and urine of normal subjects (273). Since the earlier conflicting reports, based on assays of crude urine samples (228, 259, 272, 273), improved methods of extraction and chromatographic separation have enabled a more quantitative estimate to be made of the levels in urine. Luetscher & Axelrad (244) and Venning *et al.* (256), employing biological assay, report levels of 1.5 to 5 μg./24 hr., whereas values of 8 to 16 μg./24 hr. have been obtained by Tait *et al.* (274).

A number of clinical conditions have been reported with raised urinary titres of sodium-retaining material. These include the nephrotic syndrome (226, 227, 240, 260, 272, 275), cardiac failure (226, 229, 243, 265, 272, 273, 276), hepatic cirrhosis (265, 266, 272, 277, 278), toxaemia of pregnancy (229, 243, 259, 279), some cases of Cushing's syndrome (256, 259), malignant hypertension (280), certain cases of potassium-losing nephritis (276, 281 to 284), and a case of salt-losing nephritis with congenital adrenal hyperplasia (285). An increased excretion of S.R.F. (sodium-retaining factor) has been observed after trauma and surgical operation (156, 286).

The earlier investigations, using bioassay on crude urine samples, gave little indication as to the nature of the S.R.F. Luetscher *et al.* have now identified the sodium-retaining material in the urine of nephrotic subjects, first by a study of its behaviour in a number of chromatographic systems (273, 287), and finally by the isolation of crystalline aldosterone (240). Luetscher and his colleagues have also shown that the S.R.F. in the urine of patients with cardiac failure and hepatic cirrhosis behaves like aldosterone in a number of chromatographic systems, and that 75 per cent of the activity present in the crude extracts can be recovered from those fractions expected to contain this compound. There is, therefore, little reason to doubt that this hormone is responsible for the sodium-retaining activity found in the urine of such patients.

The identity of the S.R.F. in cases of toxaemia of pregnancy is less certain, since no chromatographic studies have yet been reported for the identi-

fication of this material. The increased yields after incubation with β glucuronidase, obtained by Venning *et al.* (259), have not been confirmed by Gordon and his colleagues (243). Both groups report that there is no correlation between the excretion of S.R.F. and 17-hydroxycorticoids. This does not exclude the possibility that corticosterone may be responsible, at least in part for such activity in view of Bush's observation of greatly increased corticosterone in one such case (220).

There are varying reports on the excretion of S.R.F. in patients with Cushing's syndrome. Normal levels have been found by Gordon *et al.* (243). However, as the assays were carried out on unfractionated extracts, the increased excretion of cortisol and cortisone, which frequently occurs in such conditions, could account for the failure to detect any sodium-retaining activity (see p. 60). Venning *et al.* report high levels of S.R.F. in two out of three patients with Cushing's syndrome and in a case of malignant adrenal tumour. The S.R.F. had been identified as aldosterone in one instance on the basis of its chromatographic behaviour (259).

All of the conditions discussed above are characterised by the presence of oedema and low urinary sodium output. The syndrome, now classified as "primary aldosteronism" by Conn (282), differs from these in that the major defect appears to be excessive renal loss of potassium with hypokalemia and hypernatremia. Adrenal tumours have been found in two such cases. Conn considers that excessive aldosterone production by these tumours is responsible for this condition, but no data for the identification of this compound have been presented. Cope and Llaurado, however, in a case of "potassium-losing nephritis" with clinical symptoms very similar to those seen in "primary aldosteronism," have provided some evidence for the identity of the S.R.F. with aldosterone. Although the patient was not explored surgically, the presence of an adrenal tumour cannot be excluded. The normal excretion of 17-hydroxycorticoids and 17-ketosteroids suggests that only the electrolyte regulating function of the adrenal gland is disturbed in such conditions. A raised output of S.R.F., associated with renal loss of potassium, has been reported by Llaurado after surgical operation (286). Venning *et al.* (256) have also observed increased excretion of S.R.F. after trauma and surgical operation which appeared four to eight days after operation. No figures for potassium excretion were given.

Although the role of aldosterone in normal metabolism and in pathological conditions is not yet fully understood, the available evidence suggests that this hormone plays a major part in the regulation of mineral metabolism by the adrenal gland. Addisonian patients have been maintained in electrolyte balance by the administration of 100 to 200 μg. aldosterone per day without excessive sodium or water retention (288 to 291). Gross & Gysel (292), even when using higher levels than those required for the maintenance of normal mineral metabolism in adrenalectomized dogs, were unable to produce any overdosage effects. Later work, however, has shown that this compound can produce changes in mineral metabolism. A lowering of the Na/K urinary ratio in intact rats, and of the salivary Na/K ratio in normal

subjects, which is dependent on the dose of aldosterone, has been reported (141, 242). Administration of larger amounts (1 mg.) has produced excessive sodium, and possibly water, retention in normal, rheumatoid, and Addisonian subjects (293 to 295). Moreover, Luetscher & Axelrad (296) have shown during sodium deprivation in normal subjects that the aldosterone output increases as the urinary sodium falls. The reduction in sodium output is not accompanied by any significant changes in glomerular filtration rate or 17-hydroxycorticoid excretion. Luetscher & Curtis conclude, therefore, that aldosterone output reflects a normal mechanism for the control of sodium balance (285).

Aldosterone has been shown to be one-third as active as cortisone in the liver glycogen deposition and in the Speris' eosinophil depletion tests (248, 297, 298). It is equipotent with cortisol in protecting adrenalectomised animals against certain types of stress (297, 299). Although aldosterone clearly has some action on carbohydrate metabolism, it is unlikely, in view of the levels present in normal peripheral blood (.08 μg. aldosterone compared with 3 μg. cortisol per 100 ml. whole blood), that it exerts any significant effect on this type of metabolism. Certain clinical reports (288 to 290) have indicated that aldosterone may have more effect on glucose tolerance and blood sugar levels than would be suggested by its potency in biological assay; more extensive studies, however, have failed to show any effects on carbohydrate or protein metabolism at the dose levels used (291, 294, 295).

The significance of increased aldosterone output in certain pathological conditions is difficult to interpret from the data at present available. Conn considers that this hormone plays a causative role only in the syndrome of "primary aldosteronism," and that the increase observed in the nephrotic, syndrome, hepatic cirrhosis, and toxaemia of pregnancy is secondary to some metabolic disturbance which results in oedema formation. Luetscher considers that the presence of oedema unaccompanied by reduced urinary sodium is not in itself a reliable index of raised aldosterone output [Luetscher & Johnson (273)]. The same inverse relationship between aldosterone levels and urinary sodium excretion exists in these pathological conditions as in normal subjects. Thus, aldosterone output is increased in those phases of disease in which urinary sodium falls and oedema formation is in progress. Although it may be suggested that the restricted sodium intake, which is usually prescribed for such diseases, may be responsible for the increased aldosterone, Luetscher has been unable to demonstrate any direct relation between sodium intake and the output of this hormone in these conditions (273). Moreover, even during restricted sodium intake, diuresis, whether spontaneous or induced by giving ACTH or cortisone, is accompanied by a reduction in aldosterone output at a time when urinary sodium excretion rises. He concludes, therefore, that this hormone is the causative factor for the sodium retention which occurs in certain phases of such diseases.

Whatever the final conclusions on the role of aldosterone in these pathological conditions may be, the clear demonstration that its output varies

independently of 17-hydroxycorticoid secretion raises the interesting question of how the secretion of this hormone is controlled.

The regulation of aldosterone secretion.—In the course of the clinical studies already discussed, it became apparent that there was no direct correlation between aldosterone output and 17-ketosteroid and 17-hydroxycorticoid excretion. Venning *et al.* (256), moreover, have been unable to detect any consistent trend in the diurnal excretion of aldosterone in normal subjects similar to that found for 17-hydroxycorticoids. These observations suggest that aldosterone secretion may not be under the same control as cortisol.

As a more direct approach to this problem, aldosterone has been measured in blood and urine after administration of ACTH. Simpson & Tait (141) have been unable to detect any significant increase in aldosterone concentration in the peripheral blood of normal subjects under conditions of ACTH stimulation which produced a three- to fourfold rise in cortisol levels. No significant change in the urinary aldosterone level of normal subjects has been observed by Venning *et al.* (259) after administration of 100 mg. ACTH, or by Luetscher and his colleagues (300) after injection of sufficient (long acting) ACTH gel to produce a fivefold increase in 17-ketosteroid and 17-hydroxycorticoid excretion. Liddle *et al.* (265) have reported a twofold increase in the sodium-retaining activity of urine extracts, compared with a tenfold rise in 17-hydroxycorticoids. A transient fall to below control values followed the withdrawal of ACTH (301). An increase in aldosterone excretion has also been observed by Venning *et al.* (256) after ACTH administration to a woman with arthritis and gout. These measurements in blood and urine clearly indicate that the response of aldosterone to ACTH stimulation differs significantly from that of cortisol and its metabolites.

The increase in sodium-retaining activity of crude urine extracts after intravenous infusion of growth hormone in four normal subjects (259) suggested that aldosterone output might be increased by this pituitary hormone. More recently Venning *et al.* (256) have failed to confirm the results of their previous experiments, although the later negative findings may be caused by loss of potency of the growth hormone preparations during storage. Singer & Stack-Dunne (302), however, have found no significant increase in the aldosterone concentration of adrenal venous effluent in intact and hypophysectomised rats after treatment with pituitary growth hormone.

As early as 1940 Swann (303) suggested that the rates of mineralo- and gluco-corticoid secretion varied independently of each other, and that the former showed comparative autonomy from pituitary control. Luetscher & Axelrad (244) have found the level of aldosterone in the urine of two patients with panhypopituitarism to be comparable with that of normal men. At the time of assay, in addition to impairment of gonadotropic and thyrotropic functions, there was an obvious deficiency in the secretion of cortisol-

like corticoids. These observations are in agreement with Swann's hypothesis, although they do not provide direct evidence that the secretion of this hormone is independent of pituitary control. The measurement of aldosterone, cortisol, and corticosterone in the adrenal venous blood of the dog (304) and rat (302) has shown that aldosterone secretion continues at a proportionately much higher level than that of cortisol (dog) or corticosterone (rat) after removal of the pituitary gland. Farrell and his collaborators (305) have measured this difference quantitatively. They have found that, whereas the aldosterone concentration remains at 66 per cent, that of cortisol falls to 10 per cent of the control values, after hypophysectomy. The intravenous infusion of 200 i.u. ACTH failed to influence significantly the rate of aldosterone production over the period that blood was collected although the concentration of cortisol was markedly increased. Singer & Stack-Dunne (302) have reported a similar, though rather more complex, situation in the rat. Two days after hypophysectomy the ratio of aldosterone to corticosterone (the dominant glucocorticoid secreted by the rat) was significantly increased, and the response of corticosterone to acute corticotropin stimulation was proportionately greater (a fiftyfold increase in corticosterone, compared with a threefold increase in aldosterone levels).

Deane, Shaw & Greep (306) suggested from evidence based on histological changes in the adrenal gland that the salt intake and treatment with DOCA could regulate mineralocorticoid secretion without the mediation of the pituitary gland. These conclusions have gained support from the work of Singer & Stack-Dunne (302), who have reported that a potassium-deficient diet or administration of DOCA reduced aldosterone production to very low levels, both in intact and hypophysectomised animals, without affecting corticosterone secretion. They considered that the action of DOCA could be the result of the electrolyte changes induced by this steroid, rather than a direct inhibition of aldosterone secretion. It should be pointed out that these authors do not consider that their experiments provide direct evidence that aldosterone production is specifically associated with the zona glomerulosa of the adrenal cortex. This question remains controversial and will not be discussed in this review.

Under the conditions of their experiments, Singer & Stack-Dunne were unable to detect any significant change in aldosterone secretion in rats fed on a low sodium diet. This diet, however, contained appreciable amounts of sodium, and these findings do not exclude the possibility that a greater restriction in sodium intake could influence the secretion of this hormone. Luetscher and his colleagues (258) have observed a tenfold rise in aldosterone excretion after sodium deprivation in normal subjects. A similar increase has also been found by Liddle *et al.* (301). Laragh & Stoerk (307), however, have reported that sodium restriction in dogs, even when the serum sodium was reduced, had little effect on aldosterone output unless supplementary potassium was given in the diet. Excess of potassium, on the other hand, produced a sevenfold increase in the sodium-retaining activity of urine extracts. They consider, therefore, that a rise in serum potassium, or a fall in

the sodium/potassium ratio, is the more important stimulus to aldosterone production. As a result of studies in man, Liddle and his colleagues (301) have suggested that volume changes in body fluids, rather than sodium concentration or total body sodium, may mediate the effect of this electrolyte on aldosterone secretion.

Whatever the final conclusion as to the relative importance of these factors may be, it is clear that electrolyte changes in the body can exert a profound influence on the rate of production of this hormone. The mechanism of this action remains to be elucidated. From the results of the animal experiments reported here, it is apparent that, although the secretion of cortisol, corticosterone, and aldosterone can continue in the absence of the pituitary gland, that of aldosterone proceeds at a proportionately much higher rate.

The failure to recognise the relative independence of mineralocorticoid secretion of either endogenous or administered adrenocorticotropin control has resulted in much confusion in the interpretation of the part played by the adrenal cortex in such diseases as the nephrotic syndrome, toxaemia of pregnancy, hepatic cirrhosis, and cardiac failure (308), and of the remissions which may follow ACTH or cortisone therapy (296).

Synthetic analogues of adrenocortical hormones.—The important discovery that the potencies of adrenocortical hormones could be enormously enhanced, and also altered in a qualitative direction, by effecting minor changes in their chemical structure, has resulted already in the preparation of two groups of compounds which promise to be of great clinical value. Other such compounds will doubtless follow.

(*a*) *The 9α-halogen derivatives:* The unusual properties of these steroids were discovered by Fried & Sabo (309), whilst investigating the synthesis of cortisol (hydrocortisone) from its biologically inactive stereoisomer, 11-epihydrocortisone. Two intermediates in this synthesis, 9α-bromo- and 9α-iodo-hydrocortisone, were found to be one-third and one-tenth as active as cortisone on liver glycogen assay in the rat (309, 310). Later, the substitution of lighter halogen atoms resulted in the more remarkable finding that the 9α-chloro- and 9α-fluoro-derivatives were much more active as glucocorticoids than their halogen-free analogues (309, 311). The very potent effects of these compounds on growth and survival in the adrenalectomised rat then led to assessment of their sodium-retaining activities, which were found to be even more enhanced than the glucocorticoid effects (312). These and other biological properties of the halogen compounds in animals have been discussed recently by Fried (313). In general, it can be said that many of them combine a high degree of mineralo- and gluco-corticoid activity, and that these potencies increase as halogen atoms of diminishing atomic weight are substituted at the 9α-position. In animals the most active glucocorticoid is 9α-fluorohydrocortisone, which has about 11 times the potency of cortisol (311), and the most active mineralocorticoid is 9α-fluorocorticosterone which is about 18 times as potent as DCA, and thereby equivalent to aldosterone (314). These compounds have been shown to

inhibit ACTH secretion in the rat, with effects which are proportional to the dose; surprisingly, these effects are not greater than those of cortisol (315).

These properties of the halogen-derivatives, more especially 9α-fluorohydrocortisone which clinically seems to be the most promising member of the group, have been confirmed in man (316 to 320). In patients with adrenal insufficiency, the effects of this compound on sodium retention are at least 100 times as great as those of cortisone or cortisol (320), and equal to, and longer acting, than those of aldosterone (317, 319). As in animals, the glucocorticoid effects are enhanced somewhat less than the mineralocorticoid (317, 318, 320), though to what extent awaits further quantitative studies. The effects may vary according to the indices adopted. Thus, the anti-inflammatory effect in rheumatoid arthritis seems to be about 10 times that of hydrocortisone (free alcohol) (294, 321, 322). Estimations based on other indices of glucocorticoid function such as the fasting blood sugar (320), the blood eosinophils (317, 318, 320), water diuresis (317, 318, 320), the electrocardiogram (320), and ACTH suppression (317, 318, 323, 324), suggest that these activities of 9α-fluorohydrocortisone are less than 100, and probably less than 50, times those of cortisone or cortisol. Furthermore, the dose needed to achieve adequate cortisone-like effects is liable to cause excessive sodium and water retention, and is therefore usually contraindicated (294, 320, 321, 322, 324).

At this early stage, there seem to be at least three circumstances in which the use of 9α-fluorohydrocortisone may offer advantages over those of other steroids. Firstly, as a substitute for deoxycortone acetate in the treatment of adrenal insufficiency, with the great advantage that it can be given orally. Doses of 0.25–0.5 mg. a day have been found enough to maintain electrolyte balance in Addisonian patients (317, 318, 320), though a small supplement of cortisone may be needed to provide an optimal sense of well-being (317, 318) and to satisfy other criteria of adequate glucocorticoid activity (320). The second use is as a suppressor of ACTH in tests of adrenal function (*supra*), with the advantage that the metabolic end-products are so few as not to interfere with the interpretation of changes in urinary 17-ketosteroid and 17-hydroxycorticoid outputs (318, 323, 324). Thirdly, this new compound has been found to have about 10 times the activity of cortisol when applied locally in the treatment of certain skin diseases (325). Excessive sodium retention has not been reported, and is unlikely to occur, by this route of administration (325).

(*b*) *The* Δ_1 *compounds: prednisone and prednisolone*: An intensive search is being made for compounds related to cortisone and cortisol which will have the anti-inflammatory actions of these hormones without their undesirable metabolic effects, such as excessive salt retention and impairment of glucose tolerance. Two new steroids in which the glucocorticoid, but not the mineralocorticoid, activities are enhanced, have recently been prepared by the Schering Corporation (326). These compounds, originally called metacortandracin (Meticorten) and metacortandralone (Meticorte-

lone), but now officially named prednisone and prednisolone, have the same chemical structure as cortisone and cortisol respectively, except for the addition of a double bond in the 1:2 position.

Biological studies have shown that these steroids have three to four times the glucocorticoid activity of cortisol, as judged by their effects on the blood eosinophils, liver glycogen deposition, and thymus involution, and about the same mineralocorticoid activity (327). Preliminary studies in man have shown both steroids to be of roughly equal potency, about four times that of cortisol or cortisone (328 to 331). Qualitatively they do not seem to differ in effects from their naturally-occurring analogues, except in not causing excessive sodium retention when given in effective therapeutic doses (328 to 331). They seem to be at least twice as active as cortisol in suppressing the adrenogenital syndrome (324), and to have three to five times the antirheumatic potency of cortisone (330 to 333). At this early stage it would be rash to try to predict the clinical advantages that these steroids may offer. Preliminary reports (331), however, suggest that their use will be accompanied by many of the side-effects, except sodium retention, which are common to glucocorticoid therapy. The possibility that steroids may ultimately be found in which the antirheumatic and glucocorticoid effects are dissociated has recently been discussed by Ward & Hench (332).

The Thyroid Gland

Triiodothyronine. Harington & Barger in 1927 pointed out that thyroxine was the only physiologically active substance which could be isolated in a pure state from the thyroid gland (334). Studies over the next two decades lent support to the conclusion that thyroxine was the only iodinated substance in the plasma, and was, therefore, probably the active thyroid hormone (335 to 337). It was not easy, however, to account for the slow rate of acceleration, and the prolonged duration, of effects from a single dose of this hormone (338). Nor was it easy to explain the fact that the metabolic activity of thyroglobulin, in which form the thyroid hormone is known to be stored within the gland, was much greater than could be predicted from its content of thyroxine (338, 339), no other physiologically active component of thyroglobulin having then been isolated.

Such was the position in 1950 when Gross, Leblond *et al.*, using chromatographic techniques, described an unknown iodinated compound in the plasma of thyroidectomised mice which had been given thyroxine labelled with I^{131} (340, 341), a finding which was soon to be confirmed in man (342). Subsequently, Gross & Pitt-Rivers identified and synthesised this compound, which proved to be 3:5:3′-L-triiodothyronine. They concluded that it was a normal constituent of the organic iodide fraction, present in both euthyroid and hyperthyroid subjects (343, 344). Concurrently, Roche and his associates had detected this substance in thyroglobulin (345), and had also synthesized it (345, 346).

Next came the surprising discovery that L-triiodothyronine was at

least five times as potent as L-thyroxine both in animal assays, including the prevention of thiouracil-induced goitre (347), and in the treatment of human myxoedema (348). These properties have been further amplified and confirmed in animals (344, 349 to 351) and in man (352 to 358), and no essential qualitative differences have yet been found between the activities of these two thyroid substances. Quantitatively, however, triiodothyronine is much more rapid and transient in its actions than is L-thyroxine in man. This is reflected by the changes which occur not only in basal metabolic rate, but also in other indices of thyroid function, such as nitrogen and water excretion, plasma cholesterol, and the electrocardiogram, after a single dose of this hormone (352 to 357). The speeds of action of these two hormones can be correlated with their rates of disappearance from the blood stream. Thus, when labelled with I^{131} and given intravenously to athyrotic patients, the half-life of L-triiodothyronine is about $2\frac{1}{2}$ days, compared with that of L-thyroxine which is from 6 to 12 days (354, 359). Likewise, the plasma protein-bound iodine of athyrotic patients soon falls to insignificant levels after a single large dose of triiodothyronine (352 to 354).

These discoveries naturally have led to a revision of existing views as to the nature of the thyroid hormone. In 1952 Gross & Pitt-Rivers suggested that triiodothyronine might represent a further stage in the biological formation of the thyroid hormone, as described by Harington, and that it might be the final and tissue-active form of the hormone (347). In support of this view, further discussed by Lerman (339), was the original observation of Gross, Leblond *et al.* (340) that a substance, now known to be triiodothyronine, was formed from I^{131}-labelled thyroxine in athyrotic mice, a finding recently confirmed in man (360). Moreover, there is known to be a deiodinating enzyme (345) in body fluids which will convert diiodotyrosine to monoiodotyrosine, and it is possible that this enzyme can also effect the removal of an iodine atom from the thyroxine molecule. Though this order of synthesis probably occurs in body fluids, there is also evidence of a direct synthesis of triiodothyronine from mono- and diiodo-tyrosine within the thyroid gland (361).

It can now be questioned whether thyroxine, in unaltered form, has any activity, it being possible that its main function is to serve as a stable reservoir for the slow liberation of triiodothyronine (353). As Lerman has pointed out (339), the presence of this last hormone in the thyroglobulin molecule may explain the discrepancy in potency, previously noted, between this complex and its content of thyroxine.

A further chapter is now being added to this fascinating story. In 1953 Pitt-Rivers tested the activities of acetic acid analogues of certain thyronine compounds (362 to 364). Though triiodo- and tetraiodo-thyroacetic acids showed only about one-tenth of the effects of L-triiodothyronine in preventing goitre, the first of these analogues was very active in raising the metabolic rate. A later and more remakable finding was the almost immediate action, not only of triiodothyroacetic acid, but also of the thyroxine ana-

logue, tetraiodothyroacetic acid, when tested in vitro. Both these compounds showed effects on the oxygen consumption of rat kidney slices which were maximal in 15 min., and had ceased after 90 min. (364). Neither thyroxine nor triiodothyronine had shown any effect on this system except after a pre-incubation period of about 12 hours. Tetraiodothyroacetic acid had a similar, though slightly slower, action on the basal metabolic rate (B.M.R.) of thyroidectomised rats (364). More recently, Lerman & Pitt-Rivers have given triiodothyroacetic acid to patients with myxoedema (365). Though daily injections of this compound caused marked clinical improvement, with loss of weight and a fall in the plasma cholesterol concentration, yet the B.M.R. and pulse rate did not rise. In view of the known rapid action of this compound, this dissociation of effects could have been due to the half-day intervals which elapsed between the injections and the B.M.R. determinations. However, using very large doses of this substance, given orally every four hours, Trotter has obtained a rise in B.M.R., as well as a decrease in the other clinical and biochemical abnormalities, in a patient with myxoedema (366).

It has been suggested (364) that these, the acetic acid derivatives, may be the forms in which the thyroid hormones act in the tissues. Much further work, however, will be needed before their true significance can be assessed, and their presence in vivo has yet to be proved.

In attempting to assess the clinical significance of L-triiodothyronine, it should be remembered that there are no qualitative differences in its actions from those of L-thyroxine, and that in thyrotoxicosis both these hormones seem to be present in the same proportions as in normal subjects (342, 343). An inability to convert thyroxine to triiodothyronine has not been reported as a cause of sporadic goitrous cretinism, though in some of these cases there seems to be an intrinsic defect in the synthesis of thyroid hormone. An organic iodine-containing substance, which was neither thyroxine nor triiodothyronine, was reported in the blood of one such case (367). In another, the thyroid gland contained abundant mono- and di-iodotyrosine but no thyroxine, though this last hormone and triiodothyronine were present in the blood (368). In this case, as in those reported by Hubble (369), the defect appears to be due to a partial block in the enzymatically controlled synthesis of thyroxine from iodinated tyrosine. In other cases of this condition (368, 370) the defect lies at an earlier stage of synthesis, and consists of a failure to iodinate tyrosine. In all cases, the goitre seems to represent a compensatory effort to relieve the deficiency resulting from failure of hormone synthesis (368).

As a long-term therapeutic measure, L-triiodothyronine would seem to offer no advantages over L-thyroxine. Its rapid onset of action may indeed contraindicate its use in the initial treatment of myxoedema associated with degenerative heart disease. On the other hand, when cardiac complications arise in patients who are already receiving this hormone, the circulatory effects subside more rapidly when treatment is stopped than after thyroxine.

In tests which are designed to suppress the pituitary thyrotropic secretion (371) triiodothyronine seems to be at least as effective as thyroxine, and should have the added advantage of a speedier action. Reports of its effects in terminal myxoedema and myxoedematous coma will be awaited with interest, as will also those of the effects of the weakly calorigenic acetic acid derivatives in the treatment of spontaneous or therapeutic myxoedema with heart disease.

Hypophysectomy in Man

In the last few years the operation of hypophysectomy, which had previously been employed only for the treatment of disease of the hypophysis, has been used in the treatment of certain types of general disease. In this section the use of hypophysectomy in the treatment of malignant disease and of advanced diabetes mellitus, the methods employed to destroy the hypophysis by radiation, and the biochemical aspects of hypophysectomy, will be reviewed. The use of hypophysectomy for the treatment of Cushing's disease and of intracranial lesions will not be discussed.

Hypophysectomy in the treatment of malignant disease.—Beatson made the pioneer observations on the control of malignant disease by hormones when he reported, in 1896, the treatment of carcinoma of the breast by oophorectomy (372, 373). It is known that many tumours of the breast and the prostate are hormone-dependent, namely that their continued growth is dependent on the presence in the body of actively secreting gonads and adrenal cortex: the rationale of hypophysectomy is primarily the removal of the hypophyseal stimulation of the secretions of the gonads and adrenal cortex. It has also been shown (374) that somatotropin has a direct stimulant action on the growth of a tumour. Pearson and his colleagues administered somatotropin to a patient who had had a hypophysectomy: the secondary deposits in bone extended, and regressed again when somatotropin administration was stopped. There is some evidence that luteotropin has a direct stimulatory action on prostatic growth (375 to 377), and that the beneficial effects of hypophysectomy on prostatic carcinoma are due to the removal of luteotropin as well as of the hormones listed above.

Archer (378) has surveyed the world literature on the cases of coincident Simmonds' disease and malignant disease. He found eight cases in females and one male. None of the women had cancer of the breast (or ovary). This finding is interesting, though based on a very small number, because almost one in three cases of cancer in women are cancer of the breast.

Hypophysectomy could not be performed for the treatment of malignant disease until it became possible to prevent the patients dying from postoperative hypopituitarism. The pioneers since 1951 in the use of hypophysectomy for the treatment of malignant disease are Olivecrona, Luft *et al.* in Stockholm (379 to 384). In their recent detailed published report they describe the results in 37 cases of carcinoma of the breast (384). Their earlier work showed that if the hypophysectomy were incomplete, or if there were

secondary deposits in the liver or brain, little improvement could be expected. If such patients, and those who died from intercurrent illness, are omitted, 23 patients remain for consideration. The operation had been performed from three to 28 months prior to the report: 13 patients were alive and 10 dead. The principle effect of the hypophysectomy, in the favourable cases, was to relieve pain and to improve the general condition of the patient: patients who had been completely incapacitated were enabled to perform their household duties and to return to a reasonably normal life. The effect on local spread of the tumour and on lung metastases was variable, but on the whole the growth of these secondary deposits ceased. There was no definite evidence that any one histological type of cancer responded more favourably except that primitive anaplastic growths were less responsive. A poor result was to be expected in women over the age of 60, in whom the tumours are not hormone-dependent. Their latest report (384) states that up to December 1954, 50 cases of carcinoma of the breast had been treated by hypophysectomy. There were three operative deaths; three deaths from intercurrent illness; 19 patients died within nine months of the operation without any improvement except slight temporary relief of pain; 11 patients died within two years of the operation, having had temporary improvement: 14 patients were still alive, with improvement in many cases for over two years. Similar results have been observed by others (386). The patients who responded noticed freedom from pain and increase in general well-being, even when the progress of the disease pathologically had not been greatly altered. Perrault's first case of carcinoma of the breast had survived one year with a favourable result (387 to 389): he has reported no details of his later cases. Driesen (392) has performed six hypophysectomies with favourable results on two patients. Other hypophysectomies for single cases have also been reported (390, 391).

Pearson and his colleagues (374) have briefly reported the results of hypophysectomy on a series of 18 patients with malignant disease. Three were improved: one female with carcinoma of the breast, one male with carcinoma of the prostate, one female with malignant melanoma. Hypophysectomy had been suggested for the treatment of malignant melanoma on the basis of the hypothesis that the tumour may be dependent on hypophyseal melanocyte-stimulating hormone (*supra*). However, no improvement was noticed in the patients with melanoma for whom Luft & Olivecrona (384) and Naffziger *et al.* (393) performed hypophysectomy. Scott reported the treatment of five cases of carcinoma of the prostate (376) in two of whom a response was obtained with relief of pain and shrinkage of the growth. Luft & Olivecrona (384) consider that hypophysectomy is preferable to adrenalectomy for the treatment of carcinoma of the prostate.

Hypophysectomy has been performed, without apparent effect, for the treatment of malignant hypertension, hypernephroma and chorioncarcinoma (380), for adrenocortical carcinoma with Cushing's syndrome (394), and for seminoma (395). It would seem reasonable to perform hypophysectomy for

the treatment of malignant exophthalmos, in order to remove the hypophyseal exophthalmos-producing substance (396). No instances, however, have yet been reported.

As Luft & Olivecrona have said (384), "The number of patients and the time of observation is too small to give an answer to the question, whether hypophysectomy offers patients with metastatic breast cancer anything further than bilateral adrenalectomy in combination with ovariectomy." The theoretical advantages of hypophysectomy over adrenalectomy and ovariectomy are that hypophysectomy removes somatotropin and luteotropin, as well as the adrenal cortical hormones (including hormones from accessory adrenal glands) and gonadal hormones. The postoperative control of the patients is also easier than after adrenalectomy. The disadvantage is the technical difficulty of the operation. Since the publication of Luft and Olivecrona's work large series of cases of carcinoma of the breast are being treated by hypophysectomy in many centres. In another two or three years the place of the operation will be known.

Destruction of the hypophysis by radioactivity.—Rasmussen and his co-workers found that they could destroy the hypophysis of a monkey by the use of yttrium^{90} in the pituitary fossa (396). Yttrium^{90} is a pure β-particle emitter. The β-particles will not pass the bone of the pituitary fossa, and the brain is undamaged. This team have inserted 4 mc. of yttrium^{90} into the human pituitary fossa, but so far the ideal distribution of the yttrium pellets to achieve total destruction of the hypophysis has not been found (397). Bergensthal, in reporting the use of 5 mc. of yttrium^{90}, said that no diabetes insipidus developed in any of his nine patients (398). It is unlikely, therefore, that complete destruction of the hypophysis was achieved. Rothenberg and his co-workers injected 10 mc. of radioactive chromic phosphate into the pituitary fossa of six patients at open operation (399): this preliminary report stated that one of the three cases of carcinoma of the breast has done well. They relieved their patients' pain, but one cannot say whether their technique (which they call hypophysicteny) caused total destruction of the hypophysis. Forrest & Brown (400) inserted 15 mc. of radon into the pituitary fossa through a nasal cannula: Cade (401) has used 10 to 20 mc. of radon. The technique is relatively simple and the patient can leave the hospital in a week. However, the use of radon, a powerful source of gamma-rays, is not without danger: the difficulty is to achieve complete destruction of the hypophysis without damaging the base of the brain and neighbouring blood vessels. Other surgeons insert 7.5 mc. of Au^{198}, which principally emits β-particles, into the pituitary fossa after surgical hypophysectomy as a precaution to destroy any possible remnants of hypophyseal tissue (386). Much more work is required before radiation therapy can safely be used for destruction of the hypophysis.

Biochemical and metabolic aspects of hypophysectomy for malignant disease.—There are four main biochemical problems concerning hypophysectomy performed for the treatment of malignant disease.

If it were known which patients would respond to hypophysectomy, i.e. which tumours were hormone-dependent, a great advance would be made. Histological study at present gives no guidance, and much work has been done on the body hormone pattern of patients who suffer from malignant disease. No definite conclusions can yet be reached and much further work is required. There is a little suggestive evidence of a difference in the 17-ketosteroid excretion pattern in hormone-dependent and hormone-independent prostatic carcinoma, but no such variability has been found for carcinoma of the breast (402).

The problem of the physician is the biochemical assessment of the patients before operation, and biochemical control after the operation. Preoperative assessment must be specially directed towards assessing whether adrenal function is normal, for 40 per cent of patients with metastasising carcinoma of the breast have secondary deposits in the adrenal glands. If there is adrenal insufficiency (or if the patient has previously had an adrenalectomy), then the management and substitution therapy of the patient must be as for a bilateral adrenalectomy. Originally Luft began cortisone replacement therapy before the operation [Luft & Olivecrona (380)], and this is still the practice in most centres. More recently, and provided that adrenal functions was normal, Luft has withheld cortisone till the day of operation (384), and has stopped cortisone replacement therapy a few days after the operation in order to perform metabolic investigations. The long-term replacement therapy is 12.5 to 25 mg. of cortisone acetate twice daily, and 0.1 to 0.2 mg. of thyroxine (1 to 2 grains of thyroid) daily. Hypophysectomies have recently been performed on two patients who previously had had bilateral adrenalectomy: presumably because aldosterone was missing, more cortisone than usual was required to maintain an adequate electrolyte balance, i.e. 25 to 50 mg. twice daily (386).

The third problem is to attempt to assess whether hypophysectomy has been complete. If fragments of hypophysis are left they can maintain normal endocrine status, and the tumours will not be affected. Reoperation is possible within three weeks of the initial operation (403). If the patient is not receiving substitution therapy, the 17-ketosteroid and the corticosteroid excretion in the urine should fall to levels too low to estimate about a week after successful hypophysectomy, and signs of adrenal failure and of hypothyroidism should develop in about three weeks. There will be an early fall in the plasma protein-bound iodine and in thyroidal uptake of I^{131}, though these indices may return to normal if hypophysectomy has not been complete (404). The eosinophil response to adrenaline may also be used as a test for remaining pituitary function (383). If the patient is receiving cortisone replacement, then estimation of the individual oestrogens in pooled urinary excretion is probably the most sensitive test for remaining pituitary function (403).

The response of water excretion to total hypophysectomy is of great interest, and has been studied in detail by the Stockholm team (383, 405), and

by others (386). The excretion of water correlates with changes in the patient's thirst. There is a considerable variation in the excretion between different patients, and in the same patient on different days, but the general pattern of response is the same. In general, after operation the daily urinary volume rises to a maximum of about three litres at the third postoperative day (first polyuric phase). The daily urinary volume then falls to the preoperative level at about the seventh day (oliguric phase). This is succeeded by a second polyuric phase, and the rate of excretion of the first polyuric phase is reached by the fourteenth day. These changes are independent of cortisone replacement therapy. If cortisone is still withheld, the daily urinary volume returns to normal by about the twenty first day, as the patient develops signs of adrenocortical deficiency; the patient cannot respond to a water load, and 24 hr. of water deprivation does not result in a concentrated urine. If cortisone is given, the daily urinary volume continues to rise to about 5 l. at about the twenty-first day, and this polyuria is maintained for about six months, when the water turnover gradually returns to normal: because of the polyuria a water load test is not possible, and, again, 24 hr. of water deprivation does not result in a concentrated urine. Pitressin replacement therapy is not essential, and need be given only if the patient's comfort requires it. A tentative explanation of these changes has been advanced (405). The normal site of production of the antidiuretic hormone (ADH) is the infundibular stalk or the hypothalamus, and the posterior lobe of the pituitary acts as a store of ADH. The polyuria is due to damage to the mechanism of secretion of ADH, and this gradually recovers; however, because of the absence of stored ADH, the patients cannot respond to the water load test. ACTH is one of the mediators of the diuretic action of the anterior lobe of the pituitary. When a hypophysectomised patient is receiving cortisone, polyuria persists because cortisone somehow lowers the urinary osmolar concentration, and, by a general metabolic effect, also increases the daily load of solutes. The cause of the oliguric interphase is not known.

Hypophysectomy in the treatment of diabetes mellitus. The first case of the Houssay phenomenon in man was noted in 1932 (406), and since then other cases have been reported [q.v. review by Poulsen (407)]. In all the same result occurred as is found in experimental animals, namely, that the removal of the source of STH and ACTH, and possibly other factors, improved the diabetes and the patient became much more insulin-sensitive.

Radiation of the hypophysis had been attempted for the treatment of diabetes mellitus with hypertension (408) but without significant effects (409).

Chabanier made the first Houssay man in 1936: in his patient hypophysectomy caused slight improvement of the diabetes (410). However, hypophysectomy was not complete. Luft, Olivecrona and their colleagues have studied a series of patients (379 to 383, 411, 412). The latest report (412) is of 17 cases. There were three operative deaths, and four other deaths: the operation is recommended for the treatment of "long-standing juvenile

diabetes with progressive malignant vascular complications" (411). The results were not favourable if the inulin clearance was less than 40 ml./min. Following operation there was a marked increase in the insulin sensitivity, a fall in the blood pressure with relief of hypertensive symptoms, and a further lowering of the glomerular filtration rate. The important effects on the eyes, where before operation vascular changes were rapidly progressing with incipient blindness, were arrest of the visual deterioration and decrease of the exudates. Biochemical control must be very careful to avoid hypoglycaemic attacks. Postoperative epilepsy is a danger but can be reduced by omitting cortisone till the day of operation. Kinsell and his co-workers have reported hypophysectomy on four patients with two deaths (413). The two survivors showed improvement of the vascular complications and a marked increase in insulin sensitivity.

Because of the risks of the operation and the difficulties of postoperative control, its place is much more doubtful than that of hypophysectomy for malignant disease. As Sprague has said (414), "The results to date must be viewed with conservatism, and the studies must be regarded as being in the field of clinical investigation of an illness for which there is no known effective method of treatment."

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OBSTETRICS[1]

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Since the advent of the sulfonamides and the antibiotics, puerperal sepsis as a cause of maternal mortality has continually declined. By a negative sort of promotion, toxemia and hemorrhage have been moved into first place as the causes of death associated with childbearing (49). While the research of the past few years has not yielded the final answer in either of these two fields, new contributions of importance have been made, meriting review and consideration.

Toxemia

The eclamptogenic toxemias of pregnancy remain a syndrome which must be described rather than a disease entity that can be defined. Although the pathophysiologic changes in this chain of events are being more and more clearly delineated by current studies, no etiology has been found and the initial defect which sets the chain of events in motion has not been discovered.

In a monograph on the hypertensive disorders of pregnancy, Page has summarized well much of the recent work attempting to locate the etiology of toxemia (38). In essence, he groups these around the hypotheses that: (*a*) the nutrition of the placenta is impaired by a decrease in the maternal blood supply to the gravid uterus; (*b*) in response to this ischemia, the placenta secretes or releases into the maternal blood stream one or more chemical substances which will cause the toxemia of pregnancy in susceptible subjects; (*c*) susceptibility may be the result of sodium retention.

This attractive hypothesis, while admittedly "slanted," does provide a possible framework for considering some of the more recent contributions. Thus, Browne & Veall (7) arrived at a figure of approximately 200 cc./min. of blood circulating through the placental bed in the toxemic patients in contrast to 600 cc. in the nontoxic patients. That this is not a universal reaction throughout the body is indicated by the finding of Munnell & Taylor (36) that the blood flow through the liver increases in toxemia. McCall has shown that the blood flow per minute through the brain is not changed in normal pregnancy nor in a toxemic pregnancy with the exception of the convulsive stage of eclampsia (31).

Accordingly, it would seem that the diminished blood flow through the placental bed is a unique disturbance to that area and lends possible support to the relative ischemia theory (37). Chesley's placental perfusates were toxic when produced under conditions of relative ischemia (10).

A chemical mediator produced by the placenta was first suggested in

[1] The survey of the literature pertaining to this review was completed in August, 1955.

1941 by Kellar & Southerland (26). This humoral source of the hypertension has been more clearly defined recently with the availability of the ganglionic blocking agents as experimental tools, and Brust (8) has produced good evidence that the arteriolar spasm of pre-eclampsia is not neurogenically mediated. Indeed, the hypotensive agents that have been introduced within the past few years have to a considerable extent served more as weapons for the physiologic study of the patient than as additions to the therapeutic armamentarium (12).

From the point of view of sodium sensitivity, it is well to note that the reproduction of "toxemia" in the rat by Masson, Corcoran & Page (30) required heavy previous salt feeding before it could be successful. The toxemic woman, like the nephrotic child or the cirrhotic adult, elaborates the recently isolated steroid, aldosterone (52) in her urine (6, 9, 18, 56). This sodium-retaining steroid, however, is not found in amounts which are proportionate to the severity of the clinical syndrome (56) and disappears during a period of diuresis (6). There is no evidence that this sodium-retaining factor is the etiology of the patient's edema, and none of the work reported to date is able to explain satisfactorily whether it is a cause of, or a sequel to, the other profound changes that are taking place in the patient's physiology (27).

Therapy.—The newer implications in the therapy of the eclamptogenic toxemias can best be considered under the headings of: (*a*) correction of the physiologic disturbance; (*b*) correction of the metabolic disturbance; (*c*) control of the convulsions; (*d*) removal of the "cause".

Correction of the physiologic disturbance.—The physiologic upset of the toxemic patient is overwhelmingly arteriolar spasm (25). As indicated above, however, there is growing agreement that this is humoral rather than neurogenic in its etiology. Accordingly, the principle lying behind the therapy of this phenomenon is that no hypotensive agent which acts at or below the level of the ganglion will be effective in combating the hypertension of the toxic pregnant patient.

Such a principle rules out papaverine, the nitrites, and adenylic acid which act on the vascular wall (55); dibenamine, tolazoline (Priscoline), phentolamine (Regitine), piperoxan (Benodaine) which are adrenergic blocking agents; as well as the ganglionic blocking agents—tetraethylammonium, hexamethonium, and others. This does make possible, however, the use of hydralazine (1-hydrazinophthalazine, Apresoline) (acting centrally), the veratrum alkaloids (probably acting on the afferent vascular reflex arc), and Rauwolfia (site of action unknown). Reports of therapeutic trials which have not observed this fundamental principle have appeared only to be withdrawn (1).

Each of these hypotensive medications has been studied with respect to the toxemic patient (3, 4, 12, 32, 34, 59) and each has its advocates. Fundamentally, however, the differences pertain chiefly to the effects on the kidney and on the urinary output.

The alkaloids of veratrum will often depress urinary volume (59), chiefly through a depression of the renal plasma flow, although this effect is not as marked in the newer products available (4, 34). Hydralazine increases the blood flow through the kidney, and recent studies have indicated that the action of the Rauwolfia alkaloids in pregnancy toxemia is parallel to that of hydralazine (12).

The various side reactions to all these drugs which become apparent in the long-term management of the patient with essential hypertension, for example, are of considerably less concern in the therapy of the acute episode represented by a fulminating pre-eclampsia. Nevertheless, to minimize the unpleasant side reactions, McCall (32) has advocated the parenteral administration of a combination of hydralazine and cryptenamine (Unitensin).

Despite the welcome addition which these agents represent in the therapy of the toxemic patient, it is well to stress that they are not the "cure" of the syndrome. Since cerebral accidents represent a finding estimated by Dieckmann (15) to be present in 15–20 per cent of all the autopsies of toxemic women, these drugs obviously should reduce the loss of life from this cause. Also, the proper display of these medications to maintain the patient slightly above her normotensive level can reduce the amount of narcosis and sedation the patient requires and, hence, relieve the fetus of the depressive effect of these medications (33).

Correction of the metabolic upset.—The metabolic upset is quite evidently the acute sodium retention and associated edema which is one of the presenting characteristics of the pregnancy toxemias. (16). The finding of the increased aldosterone excretion cited above has had, of itself, no impact on the therapy of this symptom and no new technique for combating edema and sodium retention comes from this observation (6).

The best of the therapeutic weapons and the necessary background for the proper success of many of the others is sodium restriction. Discontinuation of added table salt together with the avoidance of excessive salt addition during the preparation of foods results in a sodium chloride intake per day in the neighborhood of 3 gm. which is generous from the point of view of requirements but not infrequently well below the habitual daily use of many patients (11, 13, 16).

Ammonium chloride continues to be a useful weapon for the ambulatory care of the mild pre-eclamptic. It has practically no value if not associated with or preceded by adequate sodium intake restriction, and its dosage should be in the neighborhood of 9 gm. a day. Dosage levels below 4.5 gm. a day are not significantly effective, but its intermittent employment (three days out of seven) not infrequently results in a marked reduction in edema (60).

Although formerly the mercurial diuretics were felt to be contraindicated in the presence of mild to moderate pre-eclampsia, more recently there has been a tendency to use them occasionally and no apparent harm can be traced in these patients. The patient is preferably one who has been prepared

with preceding ammonium chloride as well as preceding sodium restriction.

Acetazoleamide, (28) the carbonic anhydrase inhibitor (Diamox), (29) will produce sodium loss and the elimination of edema fluid, as will aminometramide (Mictine) (20) in these patients. Penman's preliminary studies (41, 42) indicate that the ion exchange resins will likewise assist, provided the sodium intake is restricted. Tatum advises 50 per cent glucose parenterally, but maintains that the rate of sodium elimination is always proportionate to the urinary volume (53).

Control of the convulsions.—By and large, if the physiologic upset and the metabolic upset have been successfully combated, the patient will not have convulsions. However, this is a statement which is not 100 per cent true and, in addition, it is apparently inevitable that some few patients will still receive their first prenatal care after convulsions have started (51).

The therapeutic agent par excellence remaining available for the control of the convulsions of eclampsia is magnesium sulphate. Magnesium sulphate is a poor hypotensive agent and does not belong in the group of those substances which combat vasospasm. (22) Actually, over the past decade, pharmacologic studies of the fate of parenterally administered magnesium sulphate have lagged well behind its rather widespread clinical application (23). During the past year an excellent survey of the pharmacology of magnesium sulphate has been contributed by Pritchard (43) bringing this important field up to date. Initial doses in the neighborhood of 10 grams divided between the intramuscular and the intravenous route with four additional grams every four hours are recommended. As long as the preceding urinary output has been 25 cc. or more an hour and the patient retains her patellar reflex, the toxic side effects of magnesium sulphate can be avoided (17).

Removal of the "cause."—It is not proper to speak of the fetus, its placenta and the membranes as the cause of the eclamptogenic toxemias. Nevertheless, this entity does not occur in the absence of a pregnancy or in the absence of a very recent pregnancy (38). Furthermore, the delivery of a mother is the only therapeutic gesture that might be dignified with the term "cure," the above outlined program falling more under the heading of the "control" of the symptomatology.

The two questions in this area which invariably must be faced are: When should the pregnancy be interrupted, and by what route (transabdominally or transvaginally)? These questions can be answered only with reference to specific individual cases, and clinical studies in this area which would provide final answers are not available (21). In all clinics it undoubtedly remains true that the indications for either rupture of the membranes or for caesarean section which would apply to the nontoxemic patient are liberalized in the face of this complication. It is also true that the totally unimproved patient is not a candidate for termination of a pregnancy, either by vaginal delivery or by caesarean section (17, 19). Some form of the control measures cited above and some degree of improvement in the patient's condition is imperative.

Obstetrically Created Hemorrhagic States

If a postpartum hemorrhage is strictly defined as the loss of 500 cc. of blood associated with or immediately following the delivery of the placenta, (19) then it is probably safe to say that the majority of women who fit this definition do so on the basis of some interference with the mechanism of uterine contraction. The open placental bed is the source of most of the excessive blood loss that takes place in the immediate puerperium (5). A mechanical interference with an efficient contraction of the uterus—as with retained secundines or intramural fibromata, or a relative atonia of the myometrium based on previous overdistension, general anesthesia, acute shock, or general debility can all result in an increased blood loss from the interior of the postpartum uterus.

There has been a growing body of literature, however, which indicates that whatever may be the impact of the peripheral blood clotting mechanism on the obstetric picture, there are some instances in which the obstetric complication may have marked effect on the clot-forming mechanisms of the circulating blood.

While a variety of such defects in the hemostatic mechanisms have been reported (45) the present survey will concern itself only with the literature relative to hypofibrinogenemia. The whole field has been recently well reviewed by Ratnoff, Pritchard & Colopy (46).

The obstetric conditions which are associated with hypofibrinogenemia are predominantly: (a) missed abortion—intrauterine fetal death with retention of the dead parts of conception, (48), (b) amniotic fluid embolus (57), (c) abruptio placenta—the premature separation of the normally implanted placenta (40).

The mechanism by which these various obstetric conditions actually reduce the fibrinogen content of the circulating blood is not at the present time clearly understood. Increased fibrinolysis has been demonstrated in some cases (not as often with abruptio placenta) (35). The loss of the fibrinogen through hemorrhage or excessive utilization at the site of the placental separation has been suggested by Dieckmann (14). The hypothesis has been advanced by others that the fibrinogen is deposited in widespread intravascular clotting in the small vessels (50). It is possible that the solubility of the fibrinogen is altered as suggested by Thomas and co-workers (54). In any-event, it is well to remember that, although the advocates of each of these theories believes that the answer is presently available, the final explanation for the diminishing fibrinogen levels is at the moment purely hypothesis.

From the point of view of therapy, the difference between hypofibrinogenemia and fibrinolysis is, at the present time, unimportant (46). The therapeutic principles of importance remain: (*a*) prevention, (*b*) accuracy of diagnosis, (*c*) adequacy of replacement of fibrinogen.

Missed abortion.—The occurrence of hypofibrinogenemia in the face of the retention of the products of conception after fetal death has two prerequisites: first, that the pregnancy should have existed at least $4\frac{1}{2}$ or five

months prior to fetal death, and, secondly, that the fetus be retained at least six weeks after death in the uterus (44). Under these circumstances, preventive therapy becomes the best approach to this particular problem. Cases in which death of the fetus is diagnosed and the pregnancy had not lasted initially for as much as four months, need not, in the light of our present knowledge, be a cause for concern. On the other hand, for pregnancies of five months or more in which fetal death has been demonstrated, interruption of the pregnancy at the fifth week would avoid the threat of the declining fibrinogen level.

Amniotic fluid embolus.—The patient with amniotic fluid embolus experiences vaginal bleeding not only because of possible hypofibrinogenemia but also because she is in shock (57), and the muscular contraction during shock is no better in the myometrium than it would be in the biceps. When a decrease in the fibrinogen level has been demonstrated, replacement is in order, but unless the shock is simultaneously combated with blood transfusions, Trendelenburg position, oxygen administration, and hypertensive medications, the simple administration of the fibrinogen itself may not suffice to save these critically ill patients (47). Oxytocic medications are not contraindicated after the products of conception have been expelled from the uterus and can be of tremendous assistance in stemming the postpartum hemorrhage.

Abruptio placenta.—The premature separation of a normally implanted placenta prior to the delivery of the fetus represents an obstetric crisis occasionally associated with defects in the clotting mechanism of the circulating blood (40). Depletion of the fibrinogen levels has not been demonstrated in all of these patients (46), and it is particularly important to obtain some index of the clotting mechanism of the circulating blood in these women. The infiltration of blood among the myometrial fibers of the uterus interferes grossly with efficient contraction of the placental bed, and some of the observed hemorrhages may have no mechanism other than this.

The accurate and full determination of fibrinogen level in the circulating blood is a laboratory procedure requiring approximately an hour and is not of great assistance in the obstetric crises that have been identified in hypofibrinogenemia. For these crises, Page (39) suggested the clotting time of a mixture of normal blood with an excess of thrombin. An excess of topical thrombin (3 or 4 drops of the reconstituted solution) can be kept in the freezing unit of a refrigerator and 3 cc. of blood added to this in cases of suspected deficiencies in fibrinogen. The normal patient will clot initially and the clot will remain intact. The patient with hypofibrinogenemia forms a loose clot, which in the matter of a minute or two contracts, extruding all the red blood cells (46). Wiener, Reid & Robey (58) have advocated this red cell extrusion as a sensitive indicator of hypofibrinogenemic states.

In the presence of an established diagnosis, fibrinogen is presently available and an initial dosage level of approximately 4 gm. is agreed on (24).

Conclusions

Final answers are not available in either of the pathologic entities that have been reviewed here. However, the investigative work of the past few years has produced new understandings of the mechanisms involved and has provided new therapeutic weapons. It is to be hoped, on the one hand, that the latter will contribute to the already declining maternal mortality and, on the other hand, that continued research will bring final understanding and the ultimate answers.

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ADVANCES IN THE TREATMENT OF STERILITY[1]

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Much has been written regarding the diagnosis and treatment of sterility and many of its causes are well known. The present report records some observations made in the course of the study and treatment of childless couples who were desirous of having children. It deals primarily with a few of the problems which arise in the handling of such patients.

Usually the wife is the first to seek aid in their common problem. She is asked to bring her husband with her at her first appointment. In our studies, we find that the fault in over 50 per cent of such couples probably lies with the husband, due to his incapacity to deposit a sufficient number of normal motile spermatozoa in the vagina. Female fertility depends upon fundamental physiologic conditions being favorable: one or both oviducts must be open, the endometrium must be healthy, the ovaries should produce normal ova, and the patient should ovulate with normal frequency.

The childless couples seeking our aid are frequently called "wandering" patients as they have been interviewed, tested, and usually treated by several physicians. They are couples who are frequently diagnosed as normal with nothing wrong, yet fail to conceive. In view of their past experiences, we talk first with the husband and wife together, then separately, and after testing, again together.

After the pertinent information has been secured from both husband and wife they are told what the problem involves in the way of laboratory examinations. The husband is informed of the important role that he plays in solution of the difficulty. The couple is also told at this time that men differ in the degree of their fertility, even though they may be able to produce sperm.

An obvious barrier to procreation may exist in some couples for which there is no corrective procedure. Such cases are not the concern of this report. It deals primarily with couples whose difficulties were due to either questionable male fertility or abnormality of ovulation.

STUDIES ON THE HUSBAND

Semen Examination

As the study of semen is a simple procedure it is one of the first examinations to be undertaken. Even though the husband may submit a report of a previous examination, it has been found best to repeat this procedure by a method previously described (1). The husband is instructed to report for

[1] The survey of literature pertaining to this review was completed in December, 1955.

[2] The author was aided by grants from the Samuel S. Fels Fund.

examination after practicing abstinence for a period of five days. This period of abstinence is necessary because it requires that length of time for the sperm count to reach its maximum level; it is particularly important in those cases in which the husband is of questionable fertility. Should he, by any chance, experience a nocturnal or other emission during this period of abstinence, a new appointment is made for his examination.

The specimen should be ejaculated into a sterile wide-mouthed bottle, preferably at the laboratory where it is to be examined. The patient should be instructed to procure the entire specimen, since the evaluation of the semen depends partly upon its volume. Knowing the volume makes it possible to compute the total number of moving spermatozoa. Under no circumstances should the semen be collected in a condom. The chemical reaction that takes place between the condom and the semen will inactivate the sperm.

The average volume of semen is about 4 cc., yet it may vary from less than a drop to as much as 16 cc. If the volume of the semen is less than 2.5 cc., this fact may explain why the wife has never conceived. In such cases, the wife is advised to employ a pre-conceptional douche, such as sodium bicarbonate or nutri-sal for a period of four months. If conception fails to occur during this period, husband therapeutic insemination is frequently recommended. Fertility usually is expressed as the number of moving spermatozoa per cubic centimeter. However, since the volume of the semen varies from individual to individual, it would seem that the effectiveness of the husband is expressed better in terms of the total number of spermatozoa that he is able to deposit in the vagina. We are accustomed to defining the fertility of the husband in terms of the total number of moving spermatozoa that he can deliver, to which we apply the term "absolute motility."

As spermatozoa may vary in their speed and type of motion, it is useful to determine their average forward-moving speed. A stop watch is employed for this purpose. Normal, progressively moving spermatozoa cross one square of an erythrocyte chamber (1/20 mm.) in approximately 0.7 to 1.2 sec., with an average of 1 sec. Spermatozoa of questionable quality do not attain this speed.

Fertility Classification of the Husband

The best single characteristic in evaluating the degree of fertility of the husband is the number of forward-moving cells in the complete ejaculation (absolute motility). On the basis of this figure the individual is classified as (*a*) highly fertile, (*b*) relatively fertile, or (*c*) subfertile.

The highly fertile male possesses more than 185 million moving cells in his total ejaculation; the relatively fertile man has between 80 to 185 million moving cells. Any individual who possesses less than 80 million cells is classified as subfertile (1).

Observations indicate that the counts of the highly fertile man remain constant on re-examination. For this reason, repeat counts on highly fertile

men are rarely necessary. However, the counts of relatively fertile and subfertile men are apt to be variable; consequently re-examination of these persons is necessary before final judgement regarding their fertility can be rendered.

Individuals exhibit temporary subfertility or even sterility occasionally following illness, or because of the type of work they are doing or for other reasons. One patient, for example, had absolute motility counts of 64 million and 35 million spermatozoa after a severe throat infection which required admission to the hospital for about a week. About 15 months later his semen analysis revealed 188 million active spermatozoa and soon afterwards his wife conceived. In another subject the active spermatozoa count on first examination and second examination was very reduced. Several months later this individual became azoospermic. It was learned that he was taking steam baths regularly once a week. After discontinuation of these baths for six weeks, he had an absolute motility count of 20 million spermatozoa.

Improving the Semen Specimen

In view of the large number of relatively fertile and subfertile men, one of the most important problems is to find ways of improving spermatozoa specimens. We have had success in some cases (1), but have not achieved the desired results with several of the methods commonly in use. A few comments of our experience with these methods are included.

Gonadogens, gonadotrophins, various pituitary products, four types of vitamin E, combinations of gonadogen and vitamins, and pituitary irradiation have been administered to groups of subfertile and relatively fertile men, with the object of increasing the number and speed of spermatozoa in their semen specimens. With the exception of the pituitary irradiation, which resulted in a favorable response, all other treatments by various cooperating physicians produced no significant changes in the semen.

In order to improve the semen, various techniques for concentrating or storing spermatozoa *in vitro* have also been studied. These techniques have only occasionally been of practical value in achieving pregnancy.

Thyroid substances.—After extensive trials, we have found that preparations of desiccated thyroid and thyroglobulin produce no significant change in the semen.

Thyroid-like substances.—Work has shown in preliminary findings that L-thyroxine (2) and L-triiodothyronine (3) taken by mouth very definitely alter the quality of the semen. As detailed below these findings indicate that, with certain comparable dosages, L-thyroxine depresses sperm cell activity, whereas L-triiodothyronine stimulates it.

(*a*) L-thyroxine. With L-thyroxine administered in moderate dosages, a series of 10 subfertile men showed a definite decrease in the number of active spermatozoa. Temporary sterility reflected by complete sperm inactivity was encountered in 50 per cent of the cases sometime during the experimental period, with no recovery of cell motility occurring in several

until as long as 10 weeks following cessation of medication. A marked slowing of motility of the cells became apparent on the lowest dosage of L-throxine employed, and became progressively slower as the subjects continued on the treatment. This occurred without exception in the relatively fertile men as well as subfertile men. The spermatozoa of the relatively fertile men were not so markedly depressed and recovered more quickly following discontinuation of the medication.

(*b*) L-triiodothyronine. In another series of subfertile and relatively fertile men, delicately balanced small dosages (5 to 25 μg. daily) of L-triiodothyronine (supplied as "Cytomel" by Smith, Kline & French Laboratories, Philadelphia) caused an average increase in the active cell count over pre-treatment levels of about 50 per cent. Moreover, it caused no impairment in the drive of the cells. Dosages of L-triiodothyronine were comparable in metabolic activity to those employed in the series treated with L-thyroxine. Of the 16 subfertile men given L-triiodothyronine in this group, five pregnancies have occurred in previously childless couples during treatment, and in each of these the semen picture showed a definite improvement in speed and number at the time of conception. Within several weeks following cessation of medication the spermatic indices in L-triiodothyronine treated patients have fallen to their pre-treatment levels. It is stressed that these results, although clear-cut, are preliminary and require augmentation.

Effect of pituitary irradiation.—Pituitary irradiation in proper doses may serve to a limited degree as a means of increasing the total number of moving spermatozoa in the ejaculated semen. This work has been described previously (1).

Other procedures such as partitioning the ejaculate to concentrate sperm and centrifugation of semen have also been described previously as special procedures (1) and therefore will not be considered here.

Preservation of human spermatozoa at low temperature.—Sherman & Bunge (4) reported good percentage survival of human spermatozoa following freezing of semen. Using their technique, we have been able to confirm their findings in a number of instances in our laboratory together with the Farris method (1) of semen analysis, but with variable results. An improved method was developed in our laboratory (5) which has resulted in better and more uniform results. In 90 specimens, the average percentage survival was approximately 50 per cent. Surviving sperm cells were unaltered by the procedure as far as could be determined. In cases requiring donor therapeutic insemination, preservation of sperm may prove valuable for providing accessible, diversified donor samples. It is likely that, with further refinements, the method will become practical for clinical application.

Rebound phenomenon.—In selected cases of disturbed spermatogenesis, Charny (6) states administration of large doses of testosterone (150 to 200 mg. weekly for a total of 2400 to 2700 mg.) results in an initial depression of spermatogenesis followed by a secondary regeneration. The administra-

tion of the testosterone results in a disappearance of the spermatozoa from the ejaculate. They generally reappear three months after withdrawal of the testosterone and continue to increase for the next two or three months. Charny reports that apparently 18 per cent of those treated have responded with a favorable rebound.

STUDIES ON THE WIFE

After the degree of fertility of the husband has been established, investigation of the wife is undertaken. Thyroid function is first determined. Routine procedures consist of determination of the basal metabolic rate and the concentrations of protein-bound iodine and cholesterol in the serum. Treatment is recommended if the metabolic rate is low or if there are other indications of reduced metabolism. Thyroid treatment has been frequently observed in our laboratory to improve the character of the ovulation pattern (7), with resulting pregnancy.

If physical examination reveals no pelvic pathologic changes, one of the first steps in studying the patient is to determine the patency of her Fallopian tubes. This is carried out by the use of radio-opaque fluid or by insufflation. The former procedure is preferred for a number of reasons. It supplies more information regarding the character of the tubal lumina as well as a permanent record of the tubal status. We believe the procedure is therapeutic. Hysterosalpingography is best carried out early during the week following the end of the menstrual cycle.

Murphy & Farris (8) stress the importance of not employing too much pressure when introducing radio-opaque substances into the uterus and tubes. During the course of the injection the medium may hesitate at any point along the uterotubal pathway. There is a tendency to want to increase the pressure when such a delay is encountered, but this should not be done. Maintaining the initial gentle pressure for a number of minutes usually is sufficient to overcome the original delay.

If, at the end of a 24-hr. period, the roentgenogram reveals none of the radio-opaque medium remaining in either tube, but distributed throughout the lower pelvis, tubal patency can be assumed to be adequate for fertility even though there may have been some momentary delay in the passage of the oil at the time of injection. If any oil is found in either tube the following day, it is well to repeat the hysterosalpingography after another menstrual period. The second test may reveal better tubal patency. We have observed many of these tests performed without untoward results and have noted conceptions occurring during the same menstrual cycle in which the test was made. It has been observed that lipiodol was an important factor in making conception possible, and it is, therefore, preferred as a medium.

If it seems that conception is possible, and that the husband is relatively or highly fertile, the couple is instructed to follow a set of rules for a period of about a year, in order to discover whether conception may occur without

undertaking a detailed study of the ovulation process, or of resorting to artificial insemination as an additional aid in furthering the chances of conception.

The experience gained by the use of the rat hyperemia test has made it possible to select the optimum day for coitus. It has been discovered (9) that the most suitable day for coitus is usually two days preceding the middle of the average "menstrual month." To arrive at the length of the cycle, the lengths of the last three consecutive cycles are averaged. For example, if this figure is 28 days, one-half of this is 14 days; 14 days less two days gives the twelfth day of the cycle as being the optimum day for possible impregnation. If the average length of the cycle is 30 days, then the thirteenth cycle-day is the best one to choose. This formula, incidentally, has been found to be a much more accurate method than basal body temperature method (7, 10).

After the day for fruitful coitus is selected, the husband is instructed to abstain from intercourse on the five preceding days. He is also instructed to keep his penis in the vagina for 15 min. following ejaculation to help to retain the semen in the vagina. The couple is told to continue with this schedule for four months. Meanwhile a record should be kept of the first day of each menstrual flow, since the day for coitus is based upon the length of the average cycle. If impregnation does not occur during the first four months, the procedure should be practiced for a second four months, but on the day preceding the one originally selected as the optimal, and, if this also is unsuccessful, for another four months on the day following the originally selected day.

It is of interest to note that a practical and simple device, based upon my research findings, and called a "Conceptulator" has been designed (Davidson Associates, 50 East 42nd Street, New York, New York) for the purpose of ascertaining: (*a*) the date when conception is most likely to take place; (*b*) the fertile period; (*c*) the periods when conception is least likely to occur, and (*d*) the date of confinement. The unit should be of use to the infertile couple seeking aid.

If pregnancy fails to take place during the year in which these schedules are followed, the day of ovulation is established by the use of the rat hyperemia test.

Rat Hyperemia Test for Determining the Optimum Day for Fruitful Coitus

The rat hyperemia test (11 to 14) is carried out in the following manner: The wife is asked to drink nothing after 8:00 P.M. and to void at 11:00 P.M. She is instructed to collect the urine that she voids on arising in the morning. This is done for 10 days in the middle of her menstrual cycle. In the case of patients living at a distance, the urine can be shipped, refrigerated.

Two cc. of each day's sample are injected subcutaneously into two immature, female, Wistar white rats. At the end of two hours, the animals are killed with illuminating gas which contains 20 per cent carbon monoxide. Their ovaries are exposed against a neutral gray background, and the degree of congestion is determined by comparison with a series of graduated shades of red.

If the patient is ovulating normally, the rat ovaries will exhibit a marked degree of hyperemia for four or five consecutive days. Coitus or insemination is indicated on the last day of the color reaction. If the color of the ovaries is not deep, or fails to appear consistently from day to day, the reaction is unsatisfactory and conception is unlikely to occur. In those cases in which it becomes necessary to localize the day of ovulation by means of the rat hyperemia test, and at the same time to determine whether the ovulation reaction is normal or abnormal, it is frequently advisable to complete the treatment of the couple by placing the semen in the uterine cavity by the use of a syringe. This procedure is recommended whenever the sperm count is low or the semen volume small.

Value of Timing of Ovulation

The importance of selecting the proper day for insemination (15) is shown in Table I. Insemination performed during the fertile period with the semen of highly fertile men failed in 88 attempts when it was not carried out on the day of ovulation as predicted by the rat hyperemia test.

The rat hyperemia tests indicated that ovulation in these 88 women took place on cycle-days 8 to 18. Inseminations performed from one to four days before the predicted day of ovulation, and from one to five days after that date resulted in failure. For conception it is essential that insemination be performed precisely on the day of ovulation.

Conception may occur within a matter of hours of ovulation when the optimal time of insemination has been determined by the rat test. This may be illustrated by a case (15); Mrs. X., age 30, had been unable to conceive for four years. Physical examination revealed no pelvic abnormalities. Her basal metabolic rate was normal. Lipiodol studies indicated that her Fallopian tubes were patent, although there was some narrowing of the lumen of the right tube. The uterine mucosa showed a good secretory endometrium. Her husband was highly fertile. A control rat hyperemia test indicated that a normal ovulation occurred on cycle-day 12, probably in the late afternoon, as indicated by the fading color reaction on the last day of the test. The following month the test indicated that ovulation was occurring again on cycle-day 12 in the late afternoon. The couple was, therefore, advised to have coitus twice only on that day, at 6:00 P.M. and again at 11:00 P.M. Conception took place during this month.

Three years later the couple felt that their youngster deserved a playmate. They had coitus on cycle-day 12 at 11:00 P.M. for six consecutive

months, without success. They were then advised to perform coitus on cycle-day 12, but this time at 6:00 P.M. and again at 11:00 P.M. Conception occurred during the first cycle that these hours were used.

To quote from the wife's letter, "A very interesting fact in the matter is that, from the records I kept, I find that we had coitus on the twelfth cycle-day for the past six months, but evidently had been too late in the day. I think your advice regarding the 'matinee performance' did the trick for us."

Day of conception in relation to fertile period.—The present section deals with the identification of the day of ovulation (16) as indicated by 162 conceptions following therapeutic (donor) insemination of 128 women. The results throw light upon the fertile period.

The rat ovary hyperemia test was employed for determining the day of ovulation and insemination. Insemination was performed on this day. In the majority of instances, the semen possessed 50 or more million moving sperm per cc. or approximately 200 million in the average ejaculate.

The days of the 162 successful inseminations ranged from day 10 to 20 inclusive, of menstrual cycles which varied from 20 to 38 days in average length, as illustrated in Fig. 1. The great majority of the conceptions took place on cycle days 11 through 14. Of the 162 conceptions 42 occurred on cycle day 12, in cycles which averaged from 23 to 32 days in length. Thirty-four conceptions took place on cycle day 13. These cycles ranged from 26 to 33 days in length. Twenty-eight conceptions took place on cycle day 14, in cycles which ranged from 25 to 35 days in length. Twenty-three conceptions took place on cycle day 11. In these cases the cycles ranged from 20 to 31 days in average length. About 79 per cent of the conceptions occurred on cycle days 11 to 14, inclusive, with 26 per cent occurring on cycle day 12.

TABLE I

UNSUCCESSFUL INSEMINATIONS OF 88 WOMEN IN RELATION TO PREDICTED DAY OF OVULATION

	Before predicted day of ovulation				After predicted day of ovulation				
Number of Days	4	3	2	1	1	2	3	4	5
Number of Inseminations	1	4	2	20	55	4	1	0	1

THE AVERAGE LENGTH OF THE MENSTRUAL CYCLE

The average length of 12 consecutive cycles was computed for each of 50 patients (7, 9). The average length of the cycles was computed for 3, 6, 9 and 12 months. Each average was expressed in whole days.

The average length of any three consecutive cycles was found to be about the same as the cumulative average of that person for 6, 9 or 12 cycles.

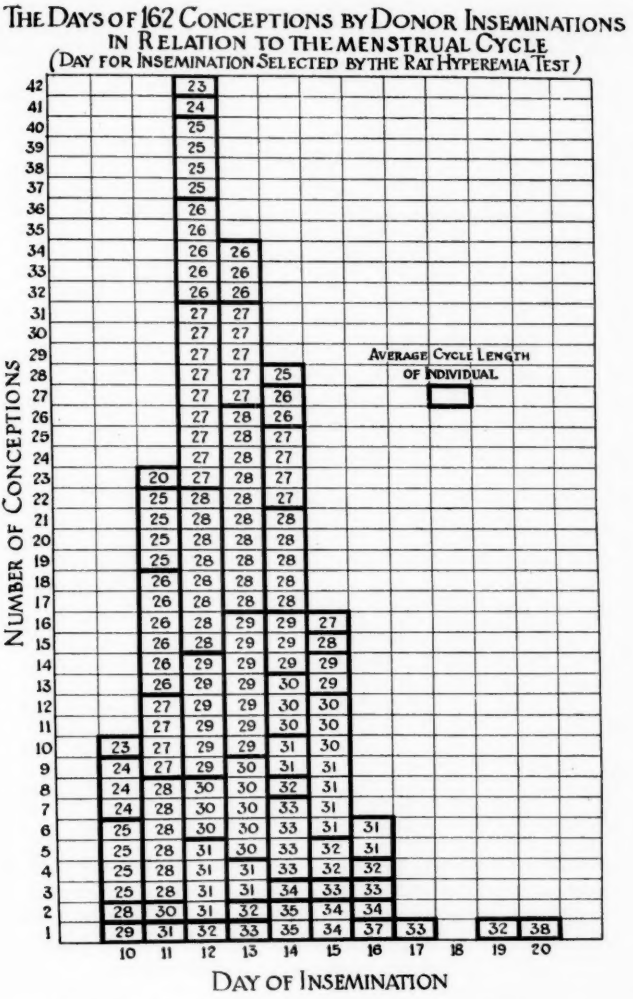

FIG. 1. Conception took place on cycle days 10 to 20 in menstrual cycles which ranged from 23 to 38 days in average cycle length. About 79 per cent of the conceptions occurred on cycle days 11 to 14. The time of ovulation was determined by the rat hyperemia test. Each individual was inseminated only once during a menstrual cycle.

TABLE II

THE DAY OF 162 CONCEPTIONS BY DONOR INSEMINATIONS IN RELATION TO THE MENSTRUAL CYCLE*

Average Length of Menstrual Cycle	No. of Conceptions	Day of Insemination											Post-Ovulatory Interval Range
		10	11	12	13	14	15	16	17	18	19	20	
20	1		1										9
23	2	1		1									11–13
24	4	3		1									12–14
25	13	4	4	4		1							11–15
26	16		6	5	3	2							12–15
27	23		4	9	5	4	1						12–16
28	31	1	6	8	10	5	1						13–18
29	19	1		6	7	3	2						14–19
30	15		1	3	5	3	3						15–19
31	15		1	4	2	2	4	2					15–20
32	7			1	1	1	2	1			1		13–20
23	8				1	4	1	1	1				16–20
34	4					1	2	1					18–20
35	2					2							21
37	1							1					21
38	1											1	18
Total	162	10	23	42	34	28	16	6	1		1	1	
Range 20–38		Range 10–20											Range 9–21

* All of the 162 conceptions occurred when insemination was performed as early as two days before the predicted day of ovulation, which day is two days before the midcycle, and as late as five days after the predicted day of ovulation.

The maximum variations in the average lengths of the cycles of 3, 6, 9 or 12 months were not over two days in most cases. The average length of any three consecutive cycles (expressed to the nearest whole day) varied so slightly from the average of more than three cycles, that only three consecutive cycles need be utilized to obtain a practical average.

DAY FOR SUCCESSFUL INSEMINATION

Table II gives the days of the inseminations which resulted in the 162 conceptions. The greatest number of the latter occurred when insemination was performed two days prior to the midcycle day. For example, in Table II, in the case of the patients who had 26 day cycles, 6 of the 16 con-

ceptions occurred when insemination took place on day 11, which was two days before the midcycle day. The next largest number, or five conceptions, took place when insemination was practiced one day before the midcycle day. The data in this table indicate that successful insemination took place most frequently one or two days prior to the midcycle day. In fact, 28 per cent of the conceptions in this series took place when insemination was performed two days before the midcycle and about 27 per cent of the conceptions occurred one day before the midcycle. All of the 162 conceptions occurred when insemination was performed as early as two days before the predicted day of ovulation, which day is two days before the midcycle (9, 16) and as late as five days after the predicted day of ovulation.

FREQUENCY OF INTERCOURSE

The foregoing information can be applied practically when the facts regarding the normal frequency of intercourse in the human male are known. In a series of over 500 couples the frequency of coitus of married white males with fertility problems averaged three times a week for those between 21 and 35 years of age, and averaged a little more than twice a week for men between 36 and 50 years of age (1).

Since "relatively fertile" and "subfertile" men are infertile unless they have a rest period of five days, it is necessary for these individuals to abstain from intercourse before the anticipated day of ovulation.

AIDS FOR THE INFERTILE COUPLE

The following recommendations are offered (*a*) Classify the men regarding their fertility on the basis of the total number of active spermatozoa in the ejaculation. (*b*) Advise the couple to abstain from intercourse for five days prior to the day of ovulation. This brings the active sperm count to its highest level. (*c*) Use the formula (or Conceptulator) for determining the ovulation date, and advise coitus on the precise day. (*d*) If the formula fails, establish ovulation day by the rat hyperemia test. (*e*) For the subfertile male, coitus is recommended twice within five to eight hours on the day of ovulation. (*f*) For the relatively fertile male, advise coitus in the late evening and the following early morning, at the approximate time of ovulation. (*g*) For the highly fertile male advise coitus for three consecutive days, beginning with the selected day of ovulation.

Application of the above observations should aid in solving some of the problems which arise in the diagnosis and treatment of sterility.

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PSYCHIATRY

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Introduction

Without doubt, the center of interest in psychiatry has focused throughout the past year upon the clinical observations pertaining to the effectiveness of a number of chemotherapeutic agents in the treatment of various psychotic and neurotic reactions. Chlorpromazine and reserpine have undergone extensive testing over a brief duration of time. Other products have been introduced and are under surveillance.

The literature upon the hallucinogenic drugs has expanded widely and numerous neurochemical hypotheses have been offered to explain the basis for their activities. Data have evolved relating to the capacity of these agents to be blocked by other chemotherapeutic products.

In addition to the pressing interest in chemotherapy and the field of experimental psychiatry, a substantial number of important studies have appeared that contribute to our knowledge of clinical psychiatry, psychotherapy, psychoanalysis, and social psychiatry.

Clinical Psychiatry

An important contribution to understanding the manic-depressive psychosis was published by Cohen and her associates (1) who conducted with psychoanalytic techniques an intensive investigation of 12 patients with this disorder. This paper provides a welcome addition to the limited number of such studies of manic-depressive reactions, and additional investigations of this kind are much needed. Its findings extend widely the data on the interpersonal factors influencing the development of these patients and also delineate the difficulties of the psychotherapeutic process with them.

Each family background of the manic-depressive, it was found, was set apart by some factor which differentiated it from others in the surrounding milieu. Such factors included membership in a minority group, unusual economic status, or particular illness. In each case the patient's family, feeling this social difference strongly, had reacted to it with intense concern. In the hope of improving the family's acceptance by the community, efforts were directed to conforming with "what the neighbors think," to raising the family's economic status, or to winning outstanding recognition in academic or other fields. Here the children of the family played the important roles: they were expected to conform to high standards of behavior, based on the family's concept of what the neighbors required. Such attitudes, particularly on the part of the mother, inculcated in the manic-depressive child a conventional concept of behavior derived from an impersonal authority. Fur-

thermore, the depersonalization of authority and the use of the child as a means of improving the family position tended to devalue the future manic-depressive child as a person in his own right. These children were raised with the idea of not "who you are" but "what you do." Thus the child destined for a manic-depressive illness was often the chief burden-bearer in the struggle to win prestige. The mother, in most instances, appeared to be the stronger and more determined parent; whereas the father, the weaker parent, was the one usually criticized for the family's unfortunate position. The child then faced the dilemma of finding the unreliable parent the lovable one and the strong, reliable parent the one disliked. In his later development the future manic-depressive was often the most highly endowed member of the family, excelling in some particular capacity which invested him with a special position in the family group. At the same time, this involved the acceptance of great responsibilities and the safeguarding of his strategic family position. It also subjected this child to the envy of the siblings and quite often to the direct competition of the parents. Thus the child grew up with exaggerated feelings of loneliness despite his development in a group-conscious atmosphere. He remained oversensitive to envy and competition, knowing well not only what it was to harbor these emotions, but also to be their target. To counteract this envy such children frequently developed early an unconscious pattern of underselling themselves in an effort to hide their full qualifications.

The major unresolved anxiety-provoking early experience of the manic-depressive appeared to arise in a crucial disturbance in interpersonal relations when his closeness (identification) with the mother was diminished, but his ability to recognize others as particular individuals had not yet unfolded. Thus in later life he would see other people as either good or bad, or black or white, and would fail to distinguish gradations.

In therapy the primary problem is the establishment of a communicative relationship between patient and physician. This is most difficult due to the patient's conventional social maneuvers, as a defence against anxiety, and to avoid emotional interchange. The manic-depressive patient in therapy must be prevented from fitting into the previous family pattern of dependency identifications, yet he must be allowed some dependency relationship. The patient's main difficulty with the physician lies in conceiving of him (and dealing with him) as a stereotype, a conventionalized authority, who is to be placated and manipulated to meet all of his dependency needs. For the therapist the problem is facing the frustration of helplessness, or attempting to communicate and move through the conventionalized social defenses of the patient.

Psychoanalysis and Psychotherapy

Giffen, Johnson & Litin (2) studied sexual aberrations in children, as well as other forms of antisocial behavior, by means of collaborative investigation in which the therapists of both parent and child reviewed together the ongoing activity of both patients in a psychoanalytically oriented treat-

ment. They again confirmed the Szurek-Johnson hypothesis that delinquent behavior in certain children represents a defect in the superego or conscience which is transmitted to the child by a parent who receives vicarious, if unconscious, satisfaction in the child's disturbed behavior. The sanction for such aberrant behavior is conveyed by the parent through innuendo in conversation with the child, errors of omission, facial expressions, or actual statements indicating that the aberrant sexual or delinquent behavior is preferable. The question as to why one child in a family is implicated in the delinquent permissiveness is not so clearly defined. A brief discussion is provided regarding the treatment of such problems by collaborative therapy.

In an effort to define those constellations of factors which lead to the eruption of overt homosexuality Kolb & Johnson (3) report the study of four adult male patients, three of whom were overtly homosexual; the fourth came for treatment for other reasons but was found to have latent homosexual impulses overtly expressed only after treatment was under way. It is interesting to note that in all of these cases the mother had been seductive toward her son, drawing him to her; yet at the same time, while stressing his feminine identification with her and unwittingly sanctioning this identification throughout his life, she had frustrated his heterosexual drives. The mother gave little real tenderness and blocked the boy's identification with his father who, due either to long-continued absences or his passivity at home, failed to protect the son from the unhealthy maternal relationship. Thus the fathers of these patients had either unconsciously or ambiguously condoned the mother's peculiar relationship with the son. The overt homosexual acting out occurred following a permissive communication indicating the mother's sanction. It was of interest that, in one instance, the overt homosexual act occurred during treatment following an unwitting, but permissive, remark of the therapist. This study disclosed in a few adults with aberrant sexual behavior the findings earlier discovered in some children.

On the basis of this study it was advised that the psychotherapeutic management of the adult patients be modified. This modification consists essentially in the nonacceptance by the psychotherapist of responsibility for the patient's overt homosexual activity. That is, the ordinary permissive relationship of the therapist to the patient may not be extended throughout treatment if the outcome is to be successful. The therapist must interpret the relationship of the patient to the therapist on the basis of the similar relationship to the permissive patient. This interpretation is presented to the patient in psychodynamic terms, indicating that the therapist does not propose to perpetuate the unhealthy permissiveness of the significant parent for the continued humiliation inherent in the patient's perverse activities. The timing of such an intervention must be carefully considered and should await the establishment of a binding transference between the patient and the therapist, and the full development of the data which discloses the parents' seductiveness and permissiveness as the factor allowing for overt homosexuality. It was the impression of the authors that for such an inter-

vention to be successful there must be no other outlets for antisocial behavior, such as pathological lying or stealing. It was suggested that perhaps the barrier to the successful treatment of many overt homosexuals was the generally permissive attitude of the ordinary psychoanalytic techniques and it was advised that a psychotherapist must be on guard lest he reinforce by passivity the permissiveness for such antisocial behavior.

In another study of the psychotherapeutic process, Whitehorn & Betz (4) examined the significance of the relationship existing between a number of physicians and their schizophrenic patients with reference to the outcome of the psychotherapeutic procedure. By studying the physician's relationship to his patient, revealed in the written notes which expressed the type of diagnostic perspective in which each physician viewed his patients, the types of strategic rôles which the physician selected as the primary focus of therapy, and the several types of tactical patterns utilized in the treatment of patients, it was found that there was a high association between improvement of the patient and particular types of physician relationship to the patient.

Those physicians who showed a good understanding of the motivation of the patient, those whose goals in treatment were aimed toward the patient's better understanding of his potentialities through the utilization of the dependable relationship between physician and patient, and finally, those physicians who participated actively and personally in treatment, were more successful in the therapy of the schizophrenic. It was found that the rates of improvement of patients treated by 14 different physicians varied remarkably. Thus the particular personality of the physician and his capacity to develop a particular type of relationship to the paient bore directly upon the therapeutic outcome. In the opinion of this reviewer, further studies of this type promise much for the future in the definition and selection of those who are to engage in successful psychotherapy. This study represents an early but ingenious effort to attack directly and to define the indicators of significant personality traits observed in action and inherent in the successful therapist for the schizophrenics. Undoubtedly the personality traits of physicians who successfully treat patients with other reaction types and by other means differ from those with aptitude for treatment of the schizophrenic. The effort of Whitehorn & Betz is a considerable advance over the attempts to define the character structure of future successful therapists by the mass application of ordinary interview techniques and by the use of a battery of selected psychological techniques.

Experimental Psychiatry

The several articles published by Lasagna *et al.* (5, 6) are of importance to those who study the effects of drugs and other chemotherapeutic agents on man. Lasagna & von Felsinger (5) examined by interview and Rorschach test a presumably healthy group of young male volunteers who presented

themselves for certain pharmacological studies. On the basis of these examinations it appeared that the volunteer group contained a high incidence of individuals with psychoneuroses, psychopathic states, alcoholism, overt homosexuality, personality disorders, and stuttering. The findings would indicate that volunteer groups are not representative of the random sample of individuals taken from a similar population. Study of the motivations for volunteering brought to light the fact that while certain volunteers undertook to participate for the monetary reward, many did so for other reasons of a psychopathological nature. In another study (6) the same workers indicate again that the highly variable subjective reactions which occur on the administration of numerous drugs may be related to differing personality structures.

Hoch (7) has succinctly reviewed the current status of investigations upon the model psychoses produced by various hallucinogenic drugs. Much of the work was performed in his laboratories. The suggestions made earlier by the Canadian workers (Hoffer, Osmund and Smythes) that psychotic-like states might be caused by adrenochrome have not been confirmed by others, who, however, were of the opinion that another metabolite of epinephrine, adrenoxin, might be an active agent in producing a psychosis. It has been found that the hallucinogenic activity of mescaline and d-LSD_{25} (d-lysergic acid diethylamide), with their properties of altering human perception and the body image, of inducing anxiety, and releasing depressive, aggressive, and paranoid trends, may be blocked by a number of other agents. Sodium amytal or pervitin (desoxyn) will neutralize the effects of both mescaline and d-LSD_{25}. While sodium amytal reduces tension, anxiety, and the autonomic responses to these drugs, pervitin was more effective than amytal in reducing the disturbances of perception for time, space, and the body image. These drugs neutralized the autonomic disturbances induced by the hallucinogenic agents, including vomiting, sweating, and tremor. Given prior to the administration of mescaline or d-LSD_{25}, amytal and pervitin together are usually only able to delay the occurrence of the experimentally induced psychotic-like state. While chlorpromazine effectively blocks the action of mescaline and d-LSD_{25}, the Rauwolfia preparations are less potent in this respect.

It has been found that both mescaline and d-LSD_{25} lead to responses in acute schizophrenics and well-preserved schizophrenics that contrast with those in the deteriorated schizophrenic patient. In the first two groups these drugs reinforce and bring out markedly the symptomatology. The deteriorated schizophrenic patients fail to respond to their administration. Patients treated by psychosurgery respond with the basic symptoms of their schizophrenic illness when given either of the hallucinogenic agents after operation. Thus it is evident that the psychotic process is qualitatively unchanged by psychosurgery although the patient's responses are quantitatively diminished.

Chemotherapy

Chlorpromazine.—Numerous clinical studies on the use of chlorpromazine [10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride], commonly known as Thorazine or Largactil, have appeared in the world literature during the past year (8 to 14). There is a general consensus that the parenteral administration of the drug is highly effective in providing prompt control of excited and disturbed patients whether such symptoms occur as manifestations of the schizophrenic, manic-depressive, or involutional psychosis reactions, the toxic-delirious and senile psychosis, or other reaction types.

Therapy is particularly indicated when the patient's behavior is punctuated by violent and aggressive outbursts, active suicidal drives, efforts at self-mutilation, or during periods of food abstention. Goldman (13) found the drug valuable in quickly terminating delirious states due to alcohol and other toxic conditions. It has been used successfully by Gatski (10) to control the disturbed behavior of emotionally maladjusted children.

The articles by Anton-Stephens (8) and Garmany *et al.* (11), expose the differences of opinion which exist as to its effectiveness in the control of psychoneurotic symptomatology. Garmany *et al.* (11) studied its usage in the psychoneuroses and found it of aid in alleviating anxiety, but ineffective in modifying such neurotic defenses as phobias and obsessive or compulsive activities. By some it has been reported as intensifying phobic symptomatology. Pain of psychogenic origin has been relieved although central pain of neurogenic origin is not well-controlled.

Following parenteral administration of the drug the initial effect observed is a transient state of drowsiness and somnolence, succeeded by continued but marked reduction in hyperactivity, but without disturbance of awareness or consciousness. Hallucinatory and delusional thought processes either subside or become less disturbing in individuals who have been ill for short periods of time. In the more chronic psychotic reactions such distorted thought and perceptual processes have not been significantly modified. Such changes have occurred after unsuccessful therapy with electric and insulin shock and in some patients who have failed to obtain a satisfactory result following lobotomy.

Many patients relapse following withdrawal of chlorpromazine. It has been suggested that the drug should be given continuously over a period of not less than six months before withdrawal is considered. The reviewer is of the opinion that in many instances such drugs may well have to be continuously administered unless other measures are taken to modify the basic personality disturbance of the psychotic or neurotic individual.

Among those who work in institutions there is a general feeling that the drug is the most useful and promising agent that is now available. While its application is now extensive and there is no doubt that the management of hospitalized psychotic patients has been greatly modified, data are not available which show that the drug has either altered the number of new admissions to institutions or led to an increase in the discharge rate. It is

unlikely that substantial or reliable figures bearing upon these questions will be available for several years. However, the movement of large bodies of psychotic patients under treatment with this and other drugs is now under close observation in certain states where excellent statistical reporting has been the habit for years. In New York State alone approximately 8,000 certified individuals are presently under treatment with chlorpromazine and reserpine.

Chlorpromazine produces various toxic reactions. With high doses some patients develop a dissociated state, appear dazed and bewildered, and may become incontinent of urine and feces. Some minor unpleasant subjective phenomena that have been noted are tachycardia, palpitation, constipation, giddiness, lassitude, weakness, dryness in the mouth, and thirst. The responses to the drug are highly variable for the individual both as regards the favorable modification of the psychiatric symptomatology and the occurrence of toxic side effects. Some individuals failed to obtain the desired response with the total daily administration of doses 300 mg. intramuscularly, while others respond to a dose as low as 50 mg. per diem.

Certain severe complications have occurred in the course of administration of this agent. A Parkinsonian-like state may appear which is relieved by withdrawal of the drug. Often this takes place concomitantly with the period in which the psychotic manifestations subside. Goldman (13) found that approximately 8 per cent of patients treated with chlorpromazine develop dermatological disorders including morbilliform and scarlatiniform lesions. Urticaria is the most characteristic manifestation and may be accompanied by edema of the face and extremities. Some individuals develop a photosensitivity during treatment, the rash breaking out following exposure to direct sunlight. Some women have suffered lactation in the absence of pregnancy.

Goldman states that jaundice occurs in as high as 3 per cent of patients on chlorpromazine therapy. Van Ommen & Brown (15) found the jaundice to be due to an intrahepatic cholestasis. One of their patients had jaundice persisting for five months. In most instances jaundice subsides when the drug is discontinued. Leukopenia and agranulocytosis have been noted in a few patients. Hodges & Lazerte (16) report a fatal case of agranulocytosis, due to treatment with chlorpromazine. Giacobini & Lassencen (12) warn against the use of this agent when patients are undergoing treatment with thiouracil, amidopyrine, or similar agents, or when heavily sedated with hypnotics or narcotics.

Reserpine.—The potent ester alkaloid of *Rauwolfia serpentina* also has been exposed to widespread clinical testing throughout the year. The 31 papers presented at the conference held early in 1955 at the New York Academy of Sciences, and published in the Annals (17), provide a comprehensive summary of our current knowledge of the physiological, pharmacological, psychological, and clinical actions of reserpine. This agent has been administered by the intravenous and intramuscular routes in 5 to 10 mg.

dosages in the very disturbed. Such administration has been accompanied by oral therapy of 1 to 3 mg. commencing with doses twice daily, the latter increased or decreased later according to the response of the patient, but usually not above the level of 10 mg. daily. If improvement results within several weeks the intramuscular reserpine is discontinued.

The indications for its usage are similar to those of chlorpromazine. The work of Kline and his group (18) makes a point of the fact that three stages may be noted in the course of treatment with reserpine. These are the sedative period, the turbulent period, and the integration period. The initial sedative period commences shortly after institution of therapy and persists 3 to 10 days. Then the turbulent period follows in which the patient's behavior becomes disturbed again and delusional and hallucinatory processes are accentuated. Such a state may persist several days to several weeks. It is emphasized that the treatment should continue vigorously and this period will subside in those who have successful outcomes. Some patients do not progress beyond the sedative phase and others fail to readjust after becoming disturbed. Such stages have not been isolated in the early or late reports by Noce *et al.* (19) or others (17). Yet the drug has apparently been discontinued after short periods in some instances because of failure to recognize its potentially helpful delayed effects.

While the drug has been applied for the most part in the schizophrenic, manic-depressive, involutional, and senile psychosis, there are several reports of its effectiveness in the therapy of Huntington's chorea (17). Drake and Ebaugh (17) found that certain obsessive patients enjoyed a reduction in their disturbing thoughts and ideas, while one compulsive handwasher who received reserpine underwent a reduction in the intensity of the recurring compulsive drive to such a degree that it was no longer a problem. Other patients have reported a reduction in neuromuscular tension and lessening of the anxiety.

Various complications have been observed when reserpine is used as a therapeutic agent. Parkinsonism may develop but subsides with discontinuance of treatment. Convulsions occur occasionally with reserpine; apparently they have been observed less frequently with chlorpromazine. The common side effects are nasal congestion, drowsiness, diarrhea, and increase in dreaming. Sexual drive has been lessened. Orthostatic hypotension has followed the parenteral administration of reserpine as it does with chlorpromazine. Recently, Fawcett and his co-workers reported at a staff meeting of the Mayo Clinic that many hypertensive patients treated with reserpine had become depressed and one such patient committed suicide. It was thought that the drug activated deeply repressed emotional forces in such patients which led to the development of the depressive symptomatology.

Bleuler & Stolls (17) as well as Kinross-Wright (17) compared the effectiveness and the complications which result from the administration of chlorpromazine and reserpine. It is apparent that both provide significant changes in behavior and mood. Patients become less anxious and agitated,

less impulsive, more relaxed and quiet. Their responsiveness to such sympoms as delusions, hallucinations, and moodiness subsides.

Chlorpromazine tends to produce euphoria in depressed patients, while reserpine fails to achieve this effect and may induce severe depression. Bleuler reports addiction to chlorpromazine and questions its possible development after administration of reserpine.

Chlorpromazine, given by the intramuscular route, leads to painful infiltrates while reserpine does not do so. While jaundice and agranulocytosis have been seen with chlorpromazine administration this has not been reported following the use of reserpine. On the other hand, the latter does cause gastrointestinal symptoms. Both drugs cause orthostatic hypotension and even collapse; bradycardia usually occurs with chlorpromazine, while tachycardia is the rule with reserpine.

The availability of the two drugs with their slightly variant effects on mood and toxicity make it possible to apply them selectively to the needs of the individual patient. Chlorpromazine provides an immediate tranquillizing effect when administered in high doses parenterally to the severely disturbed. In contrast to reserpine, the delayed turbulent states have not been described. Currently, chorpromazine appears the more effective and useful therapeutic agent for psychiatry.

Miscellaneous agents.—A series of additional chemotherapeutic agents have recently been introduced as promising in the treatment of various psychiatric disorders. Fabing (20) states that Frenquel, the gamma isomer of α-(2-piperidyl) benzhydrol hydrochloride, has been successfully employed in relieving hallucinatory and delusional experiences in alcoholic hallucinosis as well as those that occur in the induced psychosis of *d*-LSD_{25}. On the other hand, chronic schizophrenic and senile psychotic patients, as well as those with depressive and anxiety states, have not benefited from its use. Miltown (2-methyl 2-*n*-propyl-1, 3-propanediol dicarbamate) (20, 21) is effective in the treatment of anxiety neuroses, tension headaches, and neurogenic conditions of the skin. Finally, the clinical studies on α-(2-piperidyl) benzhydrol hydrochloride (22, 23) suggest that this drug offers potentialities in the treatment of the neurotic depressive reactions but is not effective in the treatment of the psychotic depressions. There is a difference of opinion as to whether it has the side effects which are commonly observed with drugs of the amphetamine series.

Schou and his co-workers (24) reported on the effective administration of lithium salts in the treatment of 38 manic patients, a beneficial action noted earlier by workers in New Zealand. Schou found that approximately one-third of the patients profited to the extent either of obtaining a decrease in the severity of the manic attack, or by prevention of recurrent attacks; the effect of these salts was essentially symptomatic in that the manic symptoms reappeared when treatment was discontinued. It was necessary to maintain the dosage level near that producing a mild intoxication. The carbonate, citrate, and chloride salts of lithium were given in dos-

ages of between 24 and 48 m.eq. per day, to sustain a serum lithium level between 0.5 and 2.0 m.eq. per litre. Here the toxic symptoms were nausea, vomiting, diarrhea, tremor of the hands, fatigue, and drowsiness. In some patients transient inversion of the T waves of the electrocardiogram was noted.

While these chemotherapeutic agents represent a significant advance in the symptomatic therapy of mental illness, none may be considered to be curative agents. Certain of these should prove highly useful in alleviating acute and chronic disturbed states and in maintaining a more adequate social adjustment over sustained periods of time. It is apparent now that various patients may be continued in psychiatric treatment on an outpatient status with the administration of chlorpromazine or reserpine. Furthermore, they may be maintained as outpatients during periods of increasing anxiety and panic that threaten to overwhelm their limited capacities to adapt. Whether it will be possible to maintain social and psychological homeostasis over long periods of time by the continued administration of such agents will become known only after more prolonged follow-up studies. The questions of addiction to these agents and the possible occurrence of permanent neurological defects due to their usage remain unanswered.

Somatic Therapies

The series of papers published by E. D. Bond and his collaborators (25 to 28) compare the late outcome of patients treated with insulin and electroshock with that of a control series managed by the methods available prior to the advent of the shock therapies. It was found that in the involutional psychotic reactions the series of patients treated by electroshock had twice the percentage of recoveries as in the group without therapy, both at the time of discharge from the hospital and five years after this discharge. On the other hand, while the initial recovery rate was greater in the manic-depressive group treated with electroshock therapy than in those untreated, it appeared that the five year recovery rate was no better in the shock-treated group than in those who did not receive shock. In a general summary of this series of studies the authors state:

> All in all when shock therapy methods are used in the great groups of patients who show no symptoms of acute or chronic brain disease there is an encouraging increase in recoveries. In psychosis due to infection there is a lessening of the number brought to a psychiatric hospital. There is a surprising amount of relief given the patients with psychoneuroses who enter a private mental hospital organized for psychotic patients. . . . Also, with many exceptions recoveries in the control group seemed more stable than those in the shock treated series.

Another paper by West *et al.* (25) reports the long-term results of insulin coma therapy given at the Pennsylvania Hospital. They conclude that, while insulin coma therapy was effective in restoring many schizophrenic patients to their pre-psychotic adjustment, this restoration to health was not accompanied by a permanent correction of the factors that predispose the patient to regress to schizophrenia.

Cortical and Subcortical Ablations and Stimulation

The publication *Studies in Schizophrenia* by the Department of Psychiatry and Neurology of Tulane University (29) summarizes the provocative work done by this research team under the leadership of Heath. The work is an attempt to test a hypothesis that in schizophrenic patients abnormal activity of the human cerebral cortex induces abnormal subcortical electrical potentials which discharge in turn to the cortex, producing effects eventually reflected in the clinical phenomena of the psychotic reaction. In the course of the study it was found that electrical potentials could be obtained from deep-lying electrodes placed in the septal area of the brain in 20 schizophrenic patients. Both spike-wave activity and slow-wave activity were recorded. These spikes were of various shapes, sizes, and frequencies. In stimulating the septal area electrically, certain patients showed increased alertness, rapidity of speech, and clarity of thought. It was considered that some improved as a result of such deep cortical electrical stimulation. The significance of these findings for schizophrenia or for psychiatry is unclear. Heath and his co-workers suggest that the findings of such electrical potentials are phenomena directly related to the schizophrenic reaction in the sense that they failed to discover such waves in deep electrical recordings from the brains of four patients dying with terminal cancer. It may be mentioned that all the patients on whom deep electrical recordings of this type were noted had been treated either by electric shock or insulin, with the exception of two, and of these one had had hypertension for many years and the other had been a diabetic. Their interpretations and findings are challenged in the discussion presented in the volume, as they have been by various other workers who find similar electrical potentials in the deeper areas of the human brain in other conditions than schizophrenia, and by neurophysiologists who have recorded somewhat similar potentials in the brains of monkeys and cats.

Bilateral anterior cingulectomy, the selective cortical ablation introduced several years ago, has not proven superior clinically to the standard lobotomy procedure, according to Tow *et al.* (30). In their follow-up examinations of 17 patients, none was discharged from the hospital and none showed the degree of improvement obtained by others who had been leukotomized. It may be mentioned that, both in the Tulane studies and in Tow's report, anatomical studies of the operated brains are not available to indicate whether the operative procedures or the placement of electrodes coincided with the localizations suggested by the various workers. The need for proper anatomical controls has been amply demonstrated over the years in earlier lobotomy investigations.

Social Psychiatry

The application of the techniques of the sociologists to psychiatry provided the publication of several excellent papers and an important book this year.

Clausen & Kohn (31) critically examined the ecological studies which

have attempted to relate social factors to mental illness. It is their opinion that ecological findings may be interpreted as successfully on the basis of the influence of genetic, cultural, or familial factors as upon the various sociological factors. Thus the data derived from such studies provide many possible interpretations. They conclude that ecological studies may serve as useful beginnings but do not provide the solutions of the etiological study of mental illness. They warn that one must utilize other techniques with potentiality for validating the interpretation of the data if significant data in respect to etiology are to be recovered.

Kohn & Clausen (32) have re-examined also the proposition that schizophrenia is the outgrowth of social isolation, a statement elaborated years ago by Faris and others. This study was done by interviewing groups of schizophrenic and manic-depressive patients who were first admitted to mental hospitals in Maryland during 1952. The group consisted of 45 schizophrenics and 13 manic-depressive patients, out of 79 first admissions from Hagerstown. Their reponses were compared with a group of healthy subjects. Assessment of social isolation was estimated by the use of an index of social participation based upon the respondent's answers to several types of questions. It was found that, while approximately a third of the schizophrenic and manic-depressive patients did give evidence of having been socially isolated between the ages of 13 and 14, in contrast to none of the normal controls, there was no indication that the isolated patients had been prevented from interacting with their peers due to lack of available playmates, excessive residential mobility, severe illness, or parental restriction. Thus they conclude that there was no evidence of a correlation between social isolation and family relationships. The data did not support the premise that social isolation in adolescence is a predisposing factor in either schizophrenia or manic-depressive psychosis. Nor did such experience seem to increase the duration of hospitalization. The conclusion reached was that social isolation is an index of illness in the individual rather than that the isolation itself predisposed to the illness. In other words, a person predisposed to these illnesses comes to feel that he does not "belong to the peer groups" and is alienated from them. Social isolation then is an indication that the individual's difficulties have become so great that he is no longer capable of functioning in an interpersonal relationship. The development of this defect was not seen as the question of social isolation per se, and must be answered by determining conditions that produce the alienation from others.

The volume, *The Mental Hospital*, by Stanton & Schwartz (33) provides a new departure as a report on the effect of social interaction on patient problems and should be read by administrators, physicians, psychotherapists, and nurses, as well as other personnel responsible for the care and treatment of the mentally ill. Of practical import is the revelation that certain types of interaction between hospital staff members in disagreement over the management of particular patients are directly responsible for outbreaks of excitement and disturbed behavior. It is suggested that, in the series of patients

observed by them, probably all who suffered pathological excitement in the course of manic, hysterical, or schizophrenic states were in direct contact with two staff members who kept secret their disagreement about the patient's management, although they were expected to communicate with each other in regard to such matters. It was found regularly that the patient's excitement greatly diminished, or disappeared, within a few hours after discussion of disagreement between these two staff members, even though the patient did not know that such a disagreement existed or that such a discussion had occurred. It was also noted that if the staff members failed to report information directly to each other when they were expected to do so, the information nevertheless proceeded from one to the other through other people. While disguised in various ways, it indicated their negation of each other. It was suggested that this type of interaction in a group is a special example of the generally recognized tendency for both patients and personnel to behave simultaneously in a fashion more or less disturbed. Considerable tension amongst staff members was evident before collective disturbances involved the patient. These disturbances indicate not only the breakdown of the communication system of the institution but also a change in the formal structure of authority, either by abdication of authority or its assumption by other than the constituted individual.

If this analysis of the origin of disturbed states in patients is correct, an effective means of locating the origin of such conditions in mental hospitals is available.

Additional observations throw light on the interpersonal disruptions effective in leading to incontinence in the mental hospital.

The reviewer is impressed with the new insights provided by the collaboration between a practicing psychiatrist and psychoanalyst with the sociologist in the examination of certain circumscribed clinical phenomena.

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PULMONARY EMPHYSEMA[1]

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A review of the recent literature on pulmonary emphysema seems appropriate at the present time, at which there has been an increasing interest in this disease. In part this is a reflection of the general emphasis on diseases affecting the older age groups and in part it is a result of the recent surge of interest in pulmonary physiology on the part of clinicians. The pathology of pulmonary emphysema is uninspiring and the roentgenologic appearance of the lungs is not dramatic. The disease does produce many alterations in the physiology of the lungs and for this reason investigation of this aspect of the disease has been most fruitful.

The description of pulmonary emphysema by Laënnec (1), which still stands as a model of writing on clinical subjects, should be read by anyone interested in the disease. Excellent reviews have been written by Kountz & Alexander (2) and by Christie (3).

Pathology

There have been relatively few recent contributions to the pathology of pulmonary emphysema. Hartcroft (4) has made a major contribution to the understanding of the microscopic anatomy of the disease. He points out the need for the fixation of the lungs in an inflated state and for the consideration of the alveoli as three-dimensional structures. The alveoli are arranged about the alveolar duct as open stalls are related to the central passage of a barn. In emphysema the alveoli are increased in diameter and decreased in depth. The alveolar duct is increased in size. The appearance of rupture of the alveolar walls is an artifact resulting from the plane of the section passing through the mouths of the alveoli.

There have also been studies of the bronchioles and vascular tree in pulmonary emphysema. One of the characteristic features of emphysema is increased resistance to air flow in the bronchial tree. Spain & Kaufman (5) made a careful study of the bronchioles in pulmonary emphysema. They found the walls of the terminal bronchioles to be thickened. The walls showed fibrosis and often inflammatory cell infiltration. The authors believe that these changes in the bronchioles are primary and that the changes in the alveoli are secondary to bronchiolar obstruction. Cudkowicz & Armstrong (6) described narrowing and obliteration of the intrapulmonary bronchial arteries in pulmonary emphysema. This resulted from medial hyperplasia and intimal thickening. Anastomoses between the bronchial and pulmonary

[1] The survey of the literature pertaining to this review was completed in March, 1955.

arteries were also noted. Whether these changes are primary or secondary is not clear. Liebow (7) described expansion of the broncho-pulmonary venous circulation with significant anastomoses with the pulmonary venous system in pulmonary emphysema. He noted an expansion of the bronchial arterial circulation rather than an obliteration.

Physiology

Mechanics of ventilation.—In the past few years there has been a marked interest in the mechanics of ventilation of the lungs in patients with emphysema. By mechanics of ventilation is meant an analysis of those forces involved in the movement of air in and out of the lungs. The principles involved were originally formulated by Rohrer (8), and have been reviewed more recently by Fenn (9). One of the reasons for recent advances in this field has been the demonstration that intraesophageal pressure is a reasonably accurate measure of intrathoracic pressure (10 to 13, 16). The technique has obviated the use of intrapleural pressure measurements which are dangerous in patients with emphysema.

Measurement of the elastic or retractive force of the lung is of particular interest in emphysema. If the lungs are removed from the body and inflated by increasing the air pressure in the trachea, a pressure-volume curve can be constructed. This curve is approximately linear in its midportion; this means that the change in volume is proportional to the change in pressure. Such a curve can be expressed as change in pressure in cm. of water per 100 ml. change in volume of the lung or as volume change in liters associated with a pressure change of 1 cm. of water. The latter term is called compliance (13). A pressure-volume curve can be constructed in the intact animal or human being if the intrathoracic pressure and lung volume are known. The difference between the pressure in the trachea and the intrathoracic pressure under static conditions with no movement of air represents the pressure resulting from the elastic properties of the lung.

It has been known since the time of Laennec that the lungs in emphysema fail to collapse normally when the chest is opened. This has been attributed to an alteration in the elastic properties of the lungs. Stead, Fry & Ebert (14) have prepared pressure-volume curves of the lungs of patients with emphysema and compared them with curves obtained in normal human beings. Curiously enough, the general shape of the curve in emphysema does not differ widely from that found in normal human beings nor does the slope of the curve (lung compliance). This has been confirmed by others (15, 22). The characteristic finding is a shift upward of the curve associated with an increase in residual volume of the lungs. If the pressure-volume curve in the patient with emphysema is compared with that of a normal individual it will be found that less pressure is required to produce a given degree of inflation of the lung in the patient with emphysema. This alteration in the elastic properties of the lung in emphysema seems the most likely explanation for the marked increase in functional residual volume which is regularly found in

this disease. Mead, Lindgren & Gaensler (15) have described changes in compliance with increased frequency of breathing. During quiet breathing the compliance of the lungs in patients with emphysema was approximately the same as that found in normal human beings. With rapid breathing the compliance decreased in the patients with emphysema. This change did not occur in normal subjects.

It has been generally stated in clinical descriptions of emphysema that one of the characteristic features of the disease is obstruction to air flow, particularly during expiration. This obstruction to air flow is related to the marked diminution in maximum breathing capacity and one-second vital capacity. Recently there has been interest in methods for quantitative measurements of resistance to air flow in emphysema. Two methods have been used. The first method (17) involves the sudden interruption of movement of air in the respiratory system by means of a suitable valve. A rapid change in pressure occurs. It is believed that this change in pressure represents the gradient of pressure between the alveoli and mouth. The rate of air flow is recorded simultaneously by means of a pneumotachograph. By making repeated determinations at varying rates of air flow a curve relating rate of air flow to the gradient of pressure from alveoli to mouth can be constructed. This relationship is curvilinear and can be expressed by the equation $P = K_1\dot{V} + K_2\dot{V}^2$ where P is the pressure difference between alveoli and mouth and $\dot{V}$ is the rate of air flow. K_1 and K_2 are constants. The first term $K_1\dot{V}$ represents the part of the pressure required for laminar flow of air in the respiratory system and the second term $K_1\dot{V}^2$ represents the portion of the pressure required for turbulent flow. This method has been applied by Proctor, Hardy & McLean (18) to the study of patients with emphysema. An increase in resistance to air flow was noted, although this was not great in some patients. There appear to be certain inaccuracies in this method (19) and it may not be entirely reliable in the study of patients with emphysema.

A second method for measuring resistance to air flow in the respiratory system utilizes the measurement of intrathoracic pressure. The measurement includes not only resistance to air flow but also frictional resistance of the tissues of the lung. The method is based on the formula $P_T = P_L + P_V + P_P$, where P_T is the difference between intrathoracic pressure and intraoral pressure; P_L is the pressure caused by the retractive force of the lung; P_V is the pressure required to overcome tissue friction; P_P is the pressure difference between alveoli and mouth. As mentioned earlier P_L can be determined by measuring the intrathoracic pressure under static conditions. The difference between P_T and P_L then represents $P_V + P_P$. In general two techniques have been employed. Both methods employ the pneumotachograph for measurement of air flow and intraesophageal pressure or intrapleural pressure as a measure of intrathoracic pressure. In one technique P_L is obtained by measurement of intrathoracic pressure at the point of zero air flow. The measurement is made at the end of inspiration and at the end of expiration. The value of P_L between these two points can be estimated because of the linear rela-

tionship between pressure and volume. Mead & Whittenberger (13) have described an ingenious device for directly plotting rate of air flow against P_P+P_V on the face of a cathode ray tube. The method employed by Fry, Ebert, Stead & Brown (21) involves the sudden interruption of breathing by means of a valve. The difference in P_T before and after interruption represents P_P+P_V. Using these techniques the resistance to air flow plus tissue friction has been found to be markedly increased in patients with pulmonary emphysema (15, 20, 21, 22). Studies with the patients breathing an argon-oxygen mixture gave evidence that most of the increase in resistance was caused by an increase in resistance to air flow (21). Argon-oxygen has an increased density and viscosity as compared to air. As a consequence breathing this mixture will increase resistance to air flow but will not influence tissue friction. Similar studies comparing resistance on breathing a hydrogen-oxygen mixture with breathing air implied that the tissue frictional resistance was increased in emphysema (22).

An important finding in the studies of resistance to air flow in emphysema was the relationship of the position of the chest and the elastic properties of the lung to this resistance (15, 20, 21). In expiration the resistance to air flow rises to an extreme degree as the chest approaches the position of maximum expiration. Dayman (20) has discussed the reason for this striking increase in resistance. In normal individuals the intrathoracic pressure is negative and serves as a force tending to distend the bronchial tree. This is true even during expiration. As there is a slightly positive pressure in the bronchi during expiration the net force tends to distend this structure. In emphysema the intrathoracic pressure may become positive during expiration. If this pressure exceeds the pressure within the bronchial tree the bronchi will be exposed to a net pressure which will tend to collapse them. Dayman has referred to this as a check-valve mechanism. The factors which lead to positive intrathoracic pressure during expiration in patients with emphysema include increased resistance to air flow in the bronchioles and alterations in the elastic properties of the lung. For a given degree of inflation of the lungs the pressure resulting from the elastic properties of the lung (P_L) is less in a patient with emphysema than in a normal human being. Moreover, there appears to be obstruction to air flow in the bronchioles in emphysema. As a consequence the intrathoracic pressure becomes positive during expiration unless the chest is kept in a markedly hyperinflated position. Fry and coworkers (21) have formalized this concept by relating air flow, distension of the lung, and intrathoracic pressure in a three-dimensional diagram.

McIlroy & Christie (22) have constructed work diagrams from simultaneous measurements of intrathoracic pressure and rate of air flow. As one might expect, the work required to move air in and out of the lung is much increased in emphysema. The increased work is the result of the increase in nonelastic resistance. The authors suggest that the sensation of dyspnea may be related to this increase in work.

Intrapulmonary distribution of inspired gas.—Fowler (23) has described

an extremely sensitive method for determining intrapulmonary distribution of inspired gas. The subject was allowed to breathe air in a normal manner. He was then shifted to oxygen at the beginning of inspiration. The nitrogen concentration and volume flow of the succeeding expiration was then recorded. The Lilly-Hervey nitrogen meter was used to measure the nitrogen concentration in the expired air. In normal subjects the nitrogen concentration of the expired air remains relatively constant during the latter portion of expiration. This plateau is considered to represent the nitrogen concentration of alveolar gas. Even in normal subjects the nitrogen concentration of alveolar gas was slightly less at the beginning of the plateau than at the end. Patients with emphysema demonstrated a much greater variability in the concentration of nitrogen in the alveolar gas. Fowler (24) has reviewed previous work on this subject and has analyzed the possible explanations for the lack of uniformity of alveolar gas. He suggests the most likely explanation is that certain areas of the lung fill before and empty after other areas. These areas would thus contain gas inspired from the trachea and bronchi and hence would have a higher nitrogen concentration than areas which fill later. This difference in filling and emptying of different portions of the lung could be explained on the basis of variation in the elastic properties of various portions of the lung. This would explain the marked abnormality in intrapulmonary distribution of inspired gas in pulmonary emphysema.

Another method of studying intrapulmonary mixing of gases is by means of clearance curves. The subject breathes room air and is then shifted to oxygen. The decline in nitrogen concentration of the expired air in successive breaths is then followed. The mathematical basis for the analysis of these curves has been laid by Darling (25), Fowler (26), and Robertson (27). These authors point out that, if the lung were a bellows which was uniformly ventilated and if the tidal volume were constant, the nitrogen concentration of the expired air would be a simple exponential function of the number of breaths of oxygen (n). If the log of the concentration of nitrogen in the expired air were plotted against n, a straight line would be found. In practice it was found that the distribution of the gas in the lung is not uniform and hence the curve is not linear, even in normal subjects. As a result the authors considered the lung to consist of a number of different compartments, each with its own clearance rate. In emphysema there was a marked delay in the clearance of nitrogen (26).

Blair & Hickam (28) have modified this method for the study of patients with emphysema. The subject first breathes a helium-oxygen mixture for 15 min. He is then switched to oxygen and the volume and helium concentration of the expired air are measured. If the log of the helium concentration of expired air is plotted against time, the latter portion of the curve is found to be linear. This portion of the curve is assumed to represent a single, slowly but uniformly, ventilated space. The volume of this slowly ventilated space and its turnover rate are calculated from the curve. This slow space was found in some instances to comprise one-half or more of the resting lung

volume with a tenth or less of the normal total ventilation. Briscoe, Becklake & Rose (29) and Briscoe (30) have studied the mixing of helium with the functional residual volume. They also find it necessary to postulate a well-ventilated and poorly ventilated space to explain their curves.

Blood gases.—A frequent finding in the late stages of pulmonary emphysema is an increase in the carbon dioxide tension and a decrease in the oxygen saturation of the hemoglobin of the arterial blood. Many patients with dyspnea and limitation of ventilatory function consequent to pulmonary emphysema exhibit no change in the blood gases. Baldwin, Cournand & Richards (31) described 25 cases of pulmonary emphysema with definite limitation of ventilatory function in whom the oxygen saturation and carbon dioxide tension of the blood were normal at rest and on exercise. Miller, Fowler & Helmholz (32) reviewed 240 patients with pulmonary emphysema in whom measurements of arterial oxygen saturation had been made. While the incidence of hypoxemia was greater in those patients with severe symptoms than in those patients with mild symptoms, it was noted that one-third of the patients with the most severe dyspnea had normal values for arterial oxygen saturation even after exercise to the limit of tolerance.

The mechanism whereby the tension of carbon dioxide and oxygen are altered in pulmonary emphysema has excited considerable interest in the past few years. In patients with disturbance in the tension of the blood gases the resting level of ventilation tends to be slightly elevated although the oxygen consumption is approximately normal (31). There are two questions to be answered. The first is the reason for the hypoxemia and hypercapnia at rest in the presence of a relatively normal level of ventilation. The second is the failure of the level of ventilation to increase further in view of the stimulus to breathing from the elevated carbon dioxide and decreased oxygen tensions in the arterial blood.

Donald, Renzetti, Riley & Cournand (33) have given a detailed analysis of the physiologic factors involved in alterations in the blood gases. The basis for this analysis is laid in a series (34, 35, 36) of earlier papers. If all alveoli were equally ventilated and equally perfused the analysis of the exchange of gases between alveoli and blood would be simple. In general the tension of gases in the arterial blood would depend on the total alveolar ventilation, the oxygen uptake, respiratory quotient (RQ), the presence and magnitude of shunts between the pulmonary arterial and venous circulation, and the diffusion coefficient of the lungs. Unfortunately, in emphysema ventilation and perfusion of alveoli are not uniform. In fact, there is every reason to believe that some alveoli are well-ventilated and poorly perfused with blood, whereas others are poorly ventilated and well-perfused with blood. In those alveoli which are well-ventilated and poorly perfused the composition of alveolar air will approach that of inspired air. As a consequence the carbon dioxide tension will be low and the oxygen tension relatively high. In those alveoli which are poorly ventilated and well-perfused the composition of alveolar air will approach that which would obtain on equilibration with

venous blood. Hence, in those alveoli the oxygen tension will be low and the carbon dioxide tension approximately that of venous blood. The nature of the gas exchange will also vary in these two large families of alveoli. In the well-ventilated, poorly perfused alveoli large amounts of carbon dioxide will be exchanged as compared to oxygen and hence the RQ for these alveoli will be high. The reverse is true for the poorly ventilated, well-perfused alveoli.

In order to provide a basis for the analysis of these perfusion ventilation relationships in the alveoli of the lung Riley & Cournand (37) have introduced the theoretical concept of ideal alveolar air. In spite of the wide divergence in gas exchange and RQ which may occur in the separate alveoli the total gas exchange must be such that the same amount of carbon dioxide is added to the alveolar air per minute as is extracted from the venous blood, and, conversely, the same amount of oxygen must be added to venous blood per minute as is extracted from alveolar air. This is equivalent to stating that the RQ of the gas exchanged from the blood is the same as the RQ of the gas exchanged in the alveoli. Knowing this RQ and the carbon dioxide and oxygen tension of venous blood together with the appropriate oxygen and carbon dioxide dissociation curves, it is possible to plot a curve which represents the possible values for carbon dioxide tension and oxygen tension which can be found in mixed blood leaving the alveolar capillaries. If the lung is now considered as a uniformly ventilated and perfused organ, the possible values of carbon dioxide tension and oxygen tension in alveolar air which are possible for a given RQ can be plotted. The intersection of these two lines gives the oxygen tension and carbon dioxide tension of ideal alveolar air. Inasmuch as the arterial pCO_2 closely approximates the pCO_2 of ideal alveolar air, the composition of ideal alveolar air can also be calculated from the arterial pCO_2, RQ, and composition of inspired air.

Riley & Cournand (37) have used this concept of ideal alveolar air to express altered ventilation perfusion relationships as dead space admixture and venous admixture. Dead space admixture is calculated from the Bohr equation. The difference between the CO_2 content of inspired and expired air is assumed to be the result of a mixture of ideal alveolar air with inspired air. The difference between pulmonary capillary blood with gas tensions identical with ideal alveolar air and blood taken from a systemic artery is assumed to be due to admixture with mixed venous blood.

In the previous analysis it was assumed that no significant gradient existed between oxygen and carbon dioxide in the alveoli and these same gases in the blood leaving the pulmonary capillaries. In analyzing this gradient the patient is studied with high and with low tensions of oxygen in the inspired air. Because of the marked difference in the pressure gradient of oxygen between alveolar air and venous blood at high and low oxygen tensions it is possible to evaluate the factor of diffusion across the alveolar membrane.

By using the concepts described above Donald, Renzetti, Riley & Cournand (33) have studied a group of patients with pulmonary emphysema.

Almost all cases studied showed both an increase in venous admixture and dead space effect. As mentioned earlier, these changes result from alterations in the ventilation-perfusion relationships of the alveoli. The alveoli with high ventilation-perfusion ratio contribute to the dead space effect and those with a low ratio to the venous admixture effect. The term dead space as used by these authors differs from the usual concept of dead space. In normal individuals physiologic dead space corresponds in large part to the volume of gas in the conducting airways where no gas exchange occurs. Fowler (38) has evaluated dead space by a continuous measurement of the nitrogen concentration in the expired air and of the volume flow of expired gas after a breath of oxygen. There was only a slight increase in respiratory dead space in the patients with emphysema. This measurement probably in large part corresponds to the so-called anatomical dead space. This differs from the dead space measurement described by Riley and co-workers in that it does not encompass altered alveolar ventilation-perfusion relationships. Similarly the venous admixture effect described by Riley differs from measurements of true veno-arterial shunts or shunts of blood through nonventilated lung. The latter can be estimated by the method of Berggren (39). This method depends on the measurement of oxygen tension in the arterial blood by means of the polarograph while the subject is breathing pure oxygen. Using this method (40) the flow of blood through nonventilated lung in emphysema was only 5 per cent of the total pulmonary blood flow.

The diffusion of gases across the alveolar membrane is described by the diffusion coefficient. This term represents the milliliters of gas moved across the alveolar membrane of the lung per min. per mm. Hg pressure gradient. Donald, Renzetti, Riley & Cournand (33) have estimated the diffusion coefficient for oxygen in patients with emphysema. As mentioned previously, their method is dependent on the determination of the oxygen tension of arterial blood and the composition of ideal alveolar air while breathing gas of low oxygen tension and high oxygen tension. There was little change in the diffusion coefficient for oxygen in the patients with mild degree of emphysema. Patients with severe emphysema exhibited a moderate reduction in diffusion coefficient. Similar results were obtained for the lung diffusion coefficient for carbon monoxide by Kjerulf-Jensen & Kruhoffer (41).

The diffusion coefficient is related to the nature of the alveolar membrane and also to the total surface available for diffusion. It seems likely that in advanced emphysema the total surface available for diffusion is reduced as a result of the formation of bullae and the inadequate perfusion of some of the alveoli. The moderate degree of reduction of the diffusion coefficient for oxygen is not sufficient to account for any considerable reduction in oxygen saturation of the hemoglobin of the arterial blood at rest. Hence it would appear from all the evidence available that the disturbance in blood gases in emphysema is related to lack of uniformity in distribution of gases in the lung and marked variation in ventilation-perfusion relationship in the alveoli.

The regulation of the level of ventilation in emphysema is of interest and importance. In the early stages of the disease the ventilation is so regulated that the tension of carbon dioxide in the arterial blood is maintained at a normal level. In the later stages of the disease increase in pCO_2 and oxygen unsaturation of the arterial blood may develop. Numerous studies have shown that the patient with emphysema has less than a normal increase in ventilation on inhaling carbon dioxide. This is particularly true when increase in pCO_2 of the arterial blood occurs. Recently two carefully controlled studies have appeared. Prime & Westlake (42) noted that in normal subjects the mean increase in ventilation on breathing a CO_2-oxygen mixture was 2.15 l. per min. per mm. Hg rise in pCO_2, while in patients with emphysema the rise was 0.91 l. There was high degree of negative correlation between the respiratory response to CO_2 and the resting arterial pCO_2. Those patients with an elevated pCO_2 had a very limited increase in ventilation on breathing a CO_2-oxygen mixture. Tenney (43) reported similar findings. He noted a marked negative correlation between the plasma CO_2 content and increase in alveolar ventilation on breathing CO_2 oxygen mixtures. It was suggested that the failure to respond to breathing CO_2 may in large part be related to the increase in buffer base which accompanies a chronic increase in arterial pCO_2. This increase in buffer base limits the decrease in pH associated with a given increase in pCO_2 on inhalation of the CO_2 oxygen mixture. This would lead to a diminished ventilatory response according to the multiple factor theory of Gray (44). Reduction of buffer base with acetazoleamide (Diamox), however, failed to lead to the expected increase in sensitivity to CO_2 inhalation. As a result of this observation Tenney (43) concludes that the lack of response to inhaled CO_2 in emphysema can be partially but not entirely explained by the increase in buffer base. Prime & Westlake (42) concur in this opinion. It appears that the limitation in ventilatory response is caused in part by the increase in buffer base, in part by an actual decrease in sensitivity of the respiratory center to CO_2, and in part to the mechanical limitations of ventilation. In regard to the latter it is of interest that patients with severe pulmonary emphysema and increase in resting arterial pCO_2 are unable to produce a marked reduction in arterial pCO_2 with voluntary hyperventilation (45).

There is no disagreement as to the effectiveness of the anoxic stimulus to ventilation. A number of studies have been performed on the effects of breathing oxygen in patients with pulmonary emphysema and arterial oxygen unsaturation. All have found a decrease in ventilation, increase in pCO_2 and a decrease in pH (31, 42, 46, 47, 48). These studies indicate that the anoxic stimulus to ventilation mediated through the aortic and carotid bodies serves as an important mechanism in maintaining an adequate level of ventilation in patients with emphysema.

Hematologic response to anoxia.—An increase in the erythrocyte count and hemoglobin concentration of the blood regularly occurs in residents at high altitude and serves as an adaptive response. The degree of polycythemia

tends to parallel the degree of anoxia (49). Wilson, Borden & Ebert (48) have found that this hematologic response to anoxia occurs much more irregularly in patients with emphysema. The correlation between oxygen saturation of the hemoglobin of the arterial blood and the hemoglobin concentration of the blood was poor. A significant increase in the mean corpuscular volume and a decrease in the mean corpuscular hemoglobin concentration was found in patients with emphysema and anoxia. This explains the finding of a normal hemoglobin concentration and increased hematocrit reading in some patients with emphysema. The total red cell volume is increased in pulmonary emphysema and there is a high negative correlation between the increase in red cell volume and decrease in arterial oxygen saturation (50). The total blood volume may be elevated particularly in those patients with heart failure. The increase in total blood volume is almost entirely the result of increase in red cell volume.

Pulmonary circulation in pulmonary emphysema.—The presence of pulmonary arterial hypertension in patients with pulmonary emphysema has been suspected for many years because of the finding at autopsy of hypertrophy of the right ventricle. The development of the technique of cardiac catheterization has permitted direct measurements of pressure in the pulmonary circulation. The majority of patients with severe emphysema exhibit some elevation in pulmonary arterial pressure (50, 51, 52). The elevation in pressure is associated with an increase in pulmonary arterial resistance (52, 53). The "pulmonary capillary" pressure obtained by wedging a catheter in a small pulmonary artery is normal. Exercise increases the pulmonary arterial pressure (54, 55). The correlation between increase in pulmonary arterial pressure and ratio of residual volume to total lung volume is only moderate. There are emphysematous patients with severe impairment of ventilatory function who have a relatively slight increase in pulmonary arterial pressure (50, 51, 56). On the other hand, there is general agreement that there is a very high degree of negative correlation between the pulmonary arterial pressure and the arterial oxygen saturation (50, 51, 52, 56). There is also a correlation between the pulmonary arterial pressure and the pCO_2 of the arterial blood (50, 52). The mechanism of production of pulmonary hypertension in emphysema has been extensively discussed. There is general agreement that the disease reduces the size of the vascular bed. In addition it is felt that anoxia plays an important role in the production of pulmonary hypertension. This is suggested by the correlation between the degree of pulmonary hypertension and the degree of anoxia and also by the fact that, with relief of anoxia by treatment of bronchitis and bronchial obstruction, there is a fall in pulmonary arterial pressure (50, 56). There is considerable experimental evidence which suggests that anoxia may increase pulmonary arterial resistance. This has been reviewed recently (57). The administration of oxygen to patients with anoxia and pulmonary hypertension results in a decline in pressure in most instances although usually not to normal levels. There is also a decrease in calculated pulmonary arterial resistance (58, 59).

There has been considerable interest in the cardiac output in patients with pulmonary emphysema. It was originally thought that the cardiac output was increased as a mechanism of adaptation to anoxia. Recent studies have shown that the cardiac output may be high, normal, or low (50, 52, 53, 56, 60). There is a rather poor correlation between the cardiac index and degree of anoxia (50, 60). The oxygen consumption is commonly increased in pulmonary emphysema. The arteriovenous oxygen difference is normal and there is no correlation with the degree of anoxia (51, 56). Dexter *et al.* (53) have suggested that the output may fail to increase in patients with emphysema and marked hypoxia because of the increase in pulmonary vascular resistance. Fowler *et al.* (60) and Mounsey *et al.* (56) have concluded that the cardiac output in most patients with pulmonary emphysema, cor pulmonale, and heart failure is normal or slightly low. On the other hand, it is distinctly higher than in heart failure resulting from hypertensive heart disease or valvular disease of the heart. Hence this type of failure can be classified as normal output failure.

There is general agreement as to the importance of anoxia in precipitating right heart failure in patients with pulmonary emphysema. Anoxia is most commonly induced by a respiratory infection with bronchitis and bronchial obstruction. Anoxia induces a rise in pulmonary arterial pressure. Increase in blood volume, particularly red cell volume, is found. The heart dilates and there is a rise in right ventricular diastolic and systemic venous pressure. The anoxia probably interferes with myocardial function as well as increasing pulmonary arterial pressure.

The renal and cerebral circulations have also been studied in patients with pulmonary emphysema. Lewis and co-workers (61) found the renal plasma flow and glomerular filtration rate to be normal in those patients who had not been in congestive heart failure. In those patients with emphysema and congestive heart failure there was a reduction in these measurements. Patterson, Heyman & Duke (62) studied the cerebral blood flow in patients with pulmonary emphysema. They noted an increase in mean cerebral blood flow for the group compared with normal subjects. They attributed the increase to elevation in pCO_2 and decrease in pO_2 of the arterial blood. Breathing oxygen leads to a further rise in cerebral blood flow. This was attributed to the rise in pCO_2 and fall in pH. Scheinberg and co-workers (63) measured cerebral blood flow in a group of patients with moderately advanced pulmonary emphysema. They noted good correlation between arterial P_{CO_2} and cerebral blood flow although the mean value for cerebral blood flow for the group was not significantly different from normal.

Radiologic Studies

The roentgenogram of the chest is known to be unreliable in the diagnosis and assessment of the severity of pulmonary emphysema. Whitfield and co-workers (64) have evaluated the radiologic appearance of the lungs and compared these findings with measurements of the lung compartments. They noted that depression and flattening of the diaphragm and excessive

transluency of the lung fields were present in most cases but were not closely related to the severity of the disease. The respiratory movement of the diaphragm was the most valuable radiological guide to the severity of emphysema. Knott & Christie (65) conducted a critical study of radiologic diagnosis. They chose 20 patients with emphysema and selected 20 patients of similar age as a control group. The radiologic diagnosis was made by four observers, who correctly diagnosed 70 per cent of the emphysema group and 80 per cent of the control group. There was wide disagreement in assessing the degree of emphysema. Posterior-anterior and lateral films on full inspiration and full expiration were used. When diagnosis was attempted, using only a posterior-anterior film on full inspiration, the accuracy of diagnosis was much less. The roentgenographic estimation of total lung capacity was discussed by Cobb (66). He found a high degree of correlation between roentgenographic estimation of total lung capacity and a method using nitrogen clearance. By subtracting the vital capacity measured with a spirometer from the total lung capacity estimated radiologically a good estimate of the ratio of residual volume to total lung capacity was obtained.

Tests of Pulmonary Function

There have been two recent reviews of tests of pulmonary function (67, 68). The application of these tests to patients with emphysema is discussed.

Treatment

There have been numerous recent articles on the treatment of emphysema. For the most part treatment is symptomatic or palliative. Nevertheless conscientious adherence to the principles of therapy may render the patient more comfortable and prolong life. Unfortunately, little progress has been made in efforts to alter the basic physiologic defect.

The mainstay in the therapy of pulmonary emphysema is the prevention or alleviation of bronchial obstruction. As mentioned earlier, the patient with pulmonary emphysema is peculiarly vulnerable to the effects of bronchial obstruction because of the alteration in the mechanics of ventilation. Bronchial infection usually will precipitate severe dyspnea in the patient with emphysema and may lead to severe anoxia and right heart failure. The treatment of bronchial infection with antibiotics has been adequately discussed (69 to 73). The use of bronchodilating agents, administered by aerosol, has been emphasized in recent articles. Miller (74) and Segal *et al.* (69, 70) have described the proper technique of administration. Obviously these agents are much less effective in those patients who exhibit relatively little clinical evidence of bronchial obstruction. Whitfield *et al.* (75, 76) found no change in pulmonary function in patients with pulmonary emphysema, but without clinical evidence of bronchospasm, after the use of oral ephedrine or aminophylline. The use of adrenocorticotropin or cortisone is more controversial (73, 77, 78, 79). The best results occur in those patients with marked bronchospasm or with bronchial asthma. In those patients with advanced

pulmonary emphysema and little evidence of bronchospasm these agents have little effect.

Motley *et al.* (80, 81) have introduced a new method for administration of aerosols. The method employs intermittent positive pressure breathing. Positive pressure is applied to the mask during inspiration and produces inflation of the lung. The respirator cycles at the end of inspiration; the mask pressure is atmospheric during expiration, which occurs passively. It is claimed that nebulized solutions of bronchodilators are more uniformly distributed through the lungs if given in conjunction with intermittent positive pressure breathing. Good clinical results have been reported (70, 82). Recently Fowler, Helmholz & Miller (83) have conducted a study which suggests that nebulized bronchodilators are as effective given without as given with intermittent positive pressure.

The patient with emphysema has an ineffective cough mechanism. Thus there is a tendency for secretions to accumulate in the bronchial tree. Barach *et al.* (84, 85) have devised a mechanical device for aiding the elimination of secretions from the bronchi. The method is called exsufflation with negative pressure and consists of inflating the chest with positive pressure applied to a mask followed by sudden cycling to a markedly negative pressure. This produces high rate of expiratory air flow similar to that obtained with a cough. Improvement of gas exchange has been noted in patients with severe emphysema and carbon dioxide retention using exsufflation (86).

The treatment of patients with emphysema by means of breathing exercises has been the subject of several recent reports (69, 72, 87, 88). The exercises are designed to aid expiration and depend primarily on the encouragement of the use of the abdominal muscles to elevate the diaphragm. Good clinical results have been reported. Barach & Beck have used the head down position to increase elevation of the diaphragm during expiration (89). A recent report by Campbell & Friend (90) casts some doubt on the real value of exercises. The exercises had no effect on measurements of lung function. During the practice of the exercise the patient breathed slowly and in an expiratory position. The patients tended to revert to their ordinary breathing pattern when not consciously performing the exercise. Miller (101), on the other hand, claimed improved alveolar ventilation with the same level of total ventilation after exercises.

Pneumoperitoneum has been widely advocated recently in the treatment of pulmonary emphysema (91 to 96). Symptomatic improvement has been noted in some but not all patients. In most studies there appeared to be an improvement in pulmonary function. The residual volume was reduced, and the maximum breathing capacity increased. Fluoroscopy demonstrated improved movement of the diaphragm. On the other hand, a group of patients carefully studied by Becklake, Goldman & McGregor (116) showed very little improvement of pulmonary function. The improvement has been attributed to better function of the diaphragm with improved ventilation and a more effective cough. Some caution must be exercised in evaluation of these

results because of the psychological effect of the treatment. No studies have been performed on the effect of pneumoperitoneum on intrathoracic pressure. These would be of interest.

As mentioned earlier, there is excellent evidence that administration of oxygen to patients with pulmonary emphysema and hypoxia may lead to a decrease in alveolar ventilation, an increase in carbon dioxide tension, and fall in pH of the arterial blood. This may be accompanied by stupor or coma (47, 69, 73, 97). The intracranial pressure may increase (98, 99). For this reason oxygen should be administered with caution and the patient observed for this complication. The coma appears to be intimately associated with the elevation in carbon dioxide tension and associated changes in acid-base balance. Morphine and barbiturates also cause a marked fall in ventilation and increase in carbon dioxide tension of the arterial blood in patients with severe emphysema and hence should be avoided (100).

Acetazoleamide (Diamox), a carbonic anhydrase inhibitor, has been used recently to stimulate respiration in patients with severe pulmonary emphysema (102 to 106). Acetazoleamide leads to increase in urinary excretion of bicarbonate resulting in a decreased plasma bicarbonate and a hyperchloremic metabolic acidosis. This effect occurs as a result of inhibition of renal carbonic anhydrase activity. In patients with severe emphysema the decrease in plasma bicarbonate and pH may be accompanied by a decrease in arterial pCO_2 and an increase in arterial pO_2. These changes most likely result from increase in alveolar ventilation consequent to the effect of the lowered pH in the respiratory center. With very large doses of acetazoleamide, Bell *et al.* (106) noted evidence of interference with transport of carbon dioxide from the blood to the alveolar air as a result of inhibition of carbonic anhydrase activity of the red cell. While the use of acetazoleamide in emphysema is extremely interesting from the scientific viewpoint it does not appear to offer great hope as a practical mode of therapy.

The use of digitalis in emphysema is ordinarily confined to the treatment of right ventricular failure. Recent studies (56, 107) have confirmed its value under these circumstances. Administration of digitalis to patients with emphysema and right ventricular failure leads to a fall in right ventricular diastolic pressure and either an increase in cardiac output (107) or no change (56).

The surgical treatment of patients with pulmonary emphysema has been restricted. There is general agreement that large bullae which interfere with pulmonary function should be treated surgically if possible (108 to 111). Baldwin and co-workers (108) have carefully studied a group of patients with large bullae. They divide the patients into three groups. In the first group there is a large bulla which communicates freely with the bronchial tree. The function of the remaining lung is normal. This increases dead space ventilation. Surgery is optional. In the second group are large air cysts with intermittent communication with the bronchial tree; the function of the remaining lung is normal. These cysts tend to enlarge and compress adjacent

lung tissue. Surgery should be performed in this group of patients. In the third group large bullae are associated with diffuse emphysema. Indications for surgery in this group are dependent on the size of the bullae and the restriction of pulmonary function. Those patients with marked impairment of gas exchange tolerate surgery poorly. Head & Avery (112) have suggested treating these patients by inserting a catheter into the cavity followed by suction. Other surgical procedures have been suggested (113, 114). These include resection of nonperfused lung tissue, resection of sympathetic and parasympathetic nerves, and creation of collateral blood supply to the lung. Angiocardiography has been suggested as a means of defining areas of nonperfused lung tissue (114, 115).

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THE METABOLIC RESPONSE TO TRAUMA

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The response to trauma is gradually being found to be a more and more involved process. Many years ago it was thought of predominantly as a local affair, but there is now much detailed evidence of the widespread nature of the response. A thorough consideration of both local and systemic factors by a group of authors was published by Bowers in 1953 (1). During the recent conflict in Korea extensive and varied laboratory studies were carried on by members of the army medical research team on men who had been wounded or subjected to other forms of trauma. Many of these studies have been reported during the past two years, and it appears that nearly every measurable function of the body is affected by trauma and often for a surprisingly long period of time. An understanding of the response to trauma is a basic concept in all surgical fields, and it is gratifying to see the recent interest in this problem. Although it is probably not possible to separate the problems of shock from those of trauma, we have tried to avoid a direct consideration of shock in this paper.

The Hematologic Response to Trauma

An excellent review by Alexander (2) on coagulation, hemorrhage, and thrombosis has recently been published. It represents a consideration of some of the notable advances in the field. In a study of battle casualties in Korea, Crosby & Howard (3) found that, at the time of resuscitation and shortly thereafter, there was a remarkable loss of circulating red cell mass in those patients with wounds involving much tissue destruction. The authors concluded that this was due to hemolysis but the exact mechanism remains unknown. They further found that those patients receiving as much as 20 to 30 pints of stored blood (which contains high plasma hemoglobin and potassium, low labile factor, and nonviable platelets and leukocytes) in as short a time as six hours suffered little harm. Mayer (4) has also demonstrated that massive transfusions of citrated whole blood have little or no effect on the bleeding or clotting time. Scott & Crosby (5a, 5b), in a similar study of battle casualties during the first days of convalescence following wounding and resuscitation, found the platelet count and fibrinogen concentrations to be greater than normal, and the clotting time to be shorter than normal. They found also that the first stage prothrombin activity averaged 50 per cent of normal immediately after transfusion, with restoration to normal within three days followed by a secondary fall and gradual recovery. These investigators concluded that the primary fall was in some cases related

to a lack of labile factor, and that the factor responsible for the secondary fall could have been a deficiency of platelet factor III.

Cohen (6) had previously found that the increase in blood fibrinogen concentration produced by trauma in baboons could be completely prevented and actually reversed in some cases by hypophysectomy. Havens, Bock & Siegel (7) demonstrated that a severely wounded group of patients with hypoproteinemia averaged slightly greater amounts of antibody production in response to diphtheria toxoid injections than did a group of healthy controls. There was no apparent relationship between the levels of serum albumin, globulin, or total proteins, and the amount of antibody produced in either group.

Feldthusen & Lassen (8) studied serum iron levels after traumatic injuries in 10 patients, comparing the results with similar studies in eight patients with coronary occlusion They found that when the serum iron was below 60 gamma per 100 cc., all patients suffered pain and pyrexia, and exhibited eosinopenia and hypersedimentation. Low blood iron levels were found in six of the 10 cases with traumatic injury. The authors developed the concept of stress hypoferricemia.

Davis and his associates (9) studied the effect of thermal burns and whole body irradiation on clotting factors in the rat. The thermal injury alone produced a brief fall in the platelet count followed by a sustained rise. Total body irradiation in a dose of 100 r produced a brief thrombocytosis followed by a transient mild thrombocytopenia, and total body irradiation in a dose of 500 r produced a rapidly developing thrombocytopenia. Despite the enhanced mortality seen in animals receiving the combined traumata, it was apparent that the observed defective coagulation mechanism failed to account for the increased mortality. From a clinical point of view, the observed thrombocytopenia and defective clotting mechanism, as measured by the Lee-White method and by heparin clotting times, would permit the recognition of casualties in which thermal burns or other trauma were complicated by the occurrence of superimposed total body irradiation if the experimental findings are confirmed clinically. The degree of thrombocytopenia was correlated with the dose of total body irradiation.

Some Circulatory Responses to Trauma

Scott *et al.* (10) found that, when studied for vasodepressor material (VDM), the blood of injured man was found to contain large amounts, particularly after 48 hr. Muscle VDM (which differs from hepatic VDM) was not found. The amount of VDM found, however, did not correlate closely with any clinical findings. Generally, little if any VEM was found, a fact that may be related to the necessary delay in analysis.

In studying injured rats, Krâmar *et al.* (11) found an immediate rise in capillary resistance following the injury. This rise was in time followed by a drop below normal and then a gradual return to normal. In man these changes also occurred but were not as consistent as in the experimental ani-

mal. The early rise was thought probably to be due to adrenocorticotropin, for it is produced by this hormone in other contexts.

Stahl *et al.* (12) tried to evaluate autonomic nervous system activity following combat injury by measuring skin temperature, pulse volume, and finger flow before and after ulnar nerve block. They found definite evidence of sympathetic activity but were unable to determine the degree.

In some of the Korean casualties, Howard, Artz & Stahl (13) found a hypertensive response in young, normal, healthy men who had nonfatal wounds of the extremities, usually not associated with great blood loss. The response appeared to be mediated through the sympathetic system as it was blocked by regitine or hexamethonium. This hypertensive response was usually a good prognostic sign.

Prentice *et al.* (14) found that many of the Korean casualties required large amounts of blood, and, in general, those with muscle injuries required more blood. In such cases Prentice considered that continued loss into the tissues was the important factor. The role of blood transfusion as an adjunct to reparative surgery has been re-emphasized by Scott (15). He has reviewed the "when and how much" criteria, and believes that the best results are obtained by infusing a quantity of blood or plasma sufficient to raise the blood volume to 80 to 90 per cent of its normal level.

In a study of patients preoperatively and immediately after abdominal surgery, Carlsten *et al.* (16) found that the cardiac output was increased 30 to 50 per cent, the arterial oxygen saturation decreased about 5 per cent, and the arterial CO_2 saturation also decreased. The venous CO_2 was decreased, too.

In an excellent review entitled, "Body Fluid Distribution in Injury," Courtice (17) gives in detail the mechanisms of intra-extracellular and intra-extravascular fluid shifts that result from trauma to tissues, as well as the mechanism of fluid exchange with the environment. He concludes that, "the aim of these compensatory shifts in fluids is primarily to maintain the intravascular volume necessary for a normal blood pressure and for adequate circulation to the vital tissues of the organism."

A summary of fluid and electrolyte exchange in burns is presented by Bull (18) who feels that the fluid and salt disturbances in burns are part of a general process in which local tissue disturbance, and circulatory, renal, and endocrine response are all involved. Fogelman & Wilson (19) studied rates of internal water exchange in burns and other trauma. After burns the rate increased approximately three times. They ascribed this alteration to an increase in the functional capillary area available for diffusion.

Anthonisen, Hilden & Thomsen (20) report two cases of head trauma, one with traumatic cerebral edema, and the second with a fracture of the base of the skull and cerebral contusions, both of whom developed extracellular hyperosmolarity with respect to sodium and chloride. They believe that the trauma to the brain caused the hyperosmolarity by injury to a regulatory center.

Nonspecific Effects of Trauma on Organs Other than Those Directly Involved

The gastrointestinal tract.—In general, it has been noted that the gastrointestinal tract does not function well after injury. Howard *et al.* (21) found that, following injuries remote from the pancreas, the serum amylase fell below normal levels for three to five days, whereas in abdominal wounds the amylase level was apt to increase because of some injury to the pancreas, direct or indirect. The function of the gallbladder (22) was likewise decreased as measured by cholecystography. This effect lasted well over a week in the more severe cases. The effect is not primarily due to poor absorption from the bowel or failure of the liver to concentrate the dye, although both factors may play minor roles.

It has been demonstrated by Hardy (23) that gastrointestinal secretions are diminished in amount postoperatively and that this is correlated with adrenocortical function. Howard (24) also found that gastric secretion is decreased after trauma which does not involve the gastrointestinal tract directly. Salivary secretions are likewise found to be diminished.

Utilizing deuterium oxide, Howard (25) demonstrated that there was a delay in the absorption of water from the gastrointestinal tract following trauma, even after injury that did not involve the abdomen. Equilibration of the absorbed material in the body was also found to be slowed following injury, particularly if there had been a period of hypotension (26). However, following injury to the central nervous system, subcutaneous injection of deuterium oxide equilibrated more rapidly than in normals, probably because of the vasodilatation resulting from injury (27).

Drye, Schoen & Ross (28) studied the effect of nonspecific trauma on gastric secretion and on quiescent peptic ulcer, and concluded that trauma, whether surgical or accidental, tended to cause a rise in gastric acidity during the first 48 hr. Roberts (29) reported eight cases of peptic ulceration complicating surgery and trauma, with four deaths as a direct result of such ulceration. Fletcher & Harkins (30) have collected reports of 42 cases of acute peptic ulceration which developed during the course of other acute illnesses, especially after major surgery or trauma.

Scott & Howard (31) likewise found hepatic function to be depressed following injury as judged by sulfobromophthalein retention, bilirubin levels, and flocculation and turbidity tests. Those patients receiving whole blood following injury had more pronounced and prolonged changes than those receiving only plasma expanding agents. Experimentally, Nelson & Seligsohn (32) found that blood ammonia levels were higher in animals in shock, both because of higher levels in the portal venous blood and because there was less removed by the liver of an animal in shock. Ligeti *et al.* (33) found a significant decrease in the albumin and increase in the alpha 1 and alpha 2 globulin fractions in one-third of cases during the first 24 hr. following operation and in 80 per cent of cases during the next four days. The total serum

proteins and the hematocrit did not show any significant variations in the early postoperative period. These investigators also noted that in the preoperative group, the albumin tended to be lower and the globulin higher than in the healthy controls. They postulated that disturbance of the enzyme systems of the liver may be responsible for the alterations in serum proteins.

The Renal Response to Systemic Trauma

The renal response to trauma is largely related to the posttraumatic changes in the availability of adrenal cortical steroids and of antidiuretic hormone. However, there are other factors involved, of which one of the most significant is the prolonged vasoconstriction which may be associated with severe injury. Balch *et al.* (34) have discussed the management of patients with posttraumatic renal insufficiency. That there is a failure of tubular reabsorption following surgery or severe burns (35, 36) has been demonstrated by Nardi. He found an abnormal amino-aciduria consisting of the excretion of "essential" amino acids which are not normally present in the urine, as well as an increased excretion of "nonessential" amino acids. This amino-aciduria was related to, but not completely dependent upon, the degree of surgical trauma, and was considered as most likely due to a failure of tubular reabsorption. That this phenomenon is related to the level of adrenal cortical hormones is implied by the fact that a moderate degree of amino-aciduria is seen in Cushing's disease.

Roberts & Randall (37) found that the acute effects of cortisone administration in the dog were mainly an increase in the renal tubular resorption of sodium and a decrease in the phosphate reabsorption. They could find no consistent acute effects of these steroids on the renal excretion of potassium, titratable acids, and bicarbonate. However, with prolonged administration of cortisone, potassium excretion was increased and hypokalemic alkalosis was not infrequent. These authors concluded that the renal excretion of potassium may not be directly influenced by cortisone but that it might be related in part to abnormal protein and carbohydrate metabolism, cellular shifts in potassium, or other metabolic alterations.

The Endocrine Response to Trauma

Hume (38) points out the presence of a venous portal system between the median eminence of the hypothalamus and the anterior pituitary, and has good evidence to indicate that the chain of pituitary reaction really starts in the hypothalamus. Electric stimulation of this area will result in adrenocorticotropin formation. Nerve impulses stimulate the hypothalamus, which in turn releases a substance into the 'portal system' that stimulates the pituitary to form the hormone. Epinephrine will stimulate adrenocorticotropin formation, but not if there is a lesion in the hypothalamus. Therefore, it seems likely that both mental and physical stress may affect the anterior pituitary

via the hypothalamus. Of course, the pituitary hormone results in stimulation of the adrenal cortex.

McCann (39) has also done a great deal of work regarding the hypothalamic control of adrenocorticotropin release. Dudley and his co-workers (40) point out that major trauma probably stimulates the posterior pituitary, via the hypothalamus, to produce antidiuretic hormone. The well-known observation of a low urine volume after major trauma is very similar to that produced by the antidiuretic hormone and is accompanied by similar drops in serum sodium beyond what would be expected on the basis of dilution alone when salt-free solutions are given. The failure to develop a normal fluid retention in the presence of panhypopituitarism was pointed out previously by Hayes & Coller (41). The endocrine response to burn injury was discussed by Butterfield in 1954 (42). He believes that this response is not restricted to the adrenocortical effects.

The adrenal.—The importance of the adrenal cortical response to trauma has stimulated much study. The adrenal is the keystone in metabolic reactions to stress. That the adrenal response is shown by a drop in the circulating eosinophils has been confirmed by many (43 to 48). This response is attributed to the production of 11–17-oxyglucocorticoids (Compounds E and F). Howard *et al.* (46) pointed out that, under the stress of combat and without injury, eosinophil levels are usually in the low normal range. The length of of the eosinopenic response to injury varies somewhat with the type and severity of the injury (43, 44, 45). Hayes (49) points out that the drop in eosinophils indicates the adequacy of the adrenocortical response, and that, in the presence of shock, if eosinopenia does not occur, it indicates the approach of a state of irreversibility. The excretion of 17-ketosteroids as measured in the urine is apparently quite variable following trauma. It does not constantly mirror other signs of adrenal activity such as eosinopenia (47, 48, 50). The 17-hydroxycorticoids in the urine, however, at least in mild trauma, do vary inversely as a rule with the loss of nitrogen and the extent of trauma (48). Nicholas *et al.* (51) found an acid fraction of 17-ketosteroids which more closely mirrored the exciting trauma than did the rest.

Electrolyte shifts following trauma are profound. A sodium retention has been pointed out by many, as has the loss of potassium through the urine and the loss of nitrogen (37, 47, 48, 52, 53, 54). The sodium retention results in an expansion of the extracellular space which may pose a severe threat, especially for patients with poor pulmonary reserve (55). The potassium loss is profound for several days after major trauma, and these changes presumably are due to the adrenocortical hormones, although, as previously mentioned, they may represent indirect effects of the adrenal hormones on carbohydrate or protein metabolism (37).

Howard and his associates (56) carried out a study of adrenal function on 20 critically injured battle casualties during the first seven to 14 days after injury. The studies demonstrated that the stress of combat had not led to

adrenal cortical exhaustion, but each case demonstrated an adrenal cortical response to trauma. The corticosteroid excretion rose sharply following trauma, the maximum excretion sometimes not being reached until the second day after injury. If the postoperative course was uncomplicated, corticoid excretion fell to normal on the third or fourth day, and then often showed a slight secondary rise. The 24-hour excretion of 17-ketosteroids was usually normal with a few patients demonstrating a slight rise. The eosinophil count invariably fell to near zero after injury, with a return to normal in uncomplicated cases within a few days. Sometimes the count would rise above normal temporarily before leveling off. During the first 24 hr. after trauma, the plasma sodium concentration decreased and the plasma potassium concentration rose, though the latter phenomenon lasted only a few hours. Excretion of sodium and potassium following injury generally showed a retention of the former ion with excretion of more potassium than sodium, so that the sodium-potassium ratio in the urine expressed in milli-equivalents would fall to a range of between 0.5 and 0.1. The retention of sodium and loss of potassium extended over a considerable period and resulted in very marked cumulative changes as shown by balance studies.

Secondary trauma elicited a fresh response from the adrenal unless the primary response was still in progress, in which case no further increment could be recognized. Wound infection and necrosis were associated with a continued adrenocortical and electrolytic response of a magnitude and duration not seen in other casualties. The authors suggest that the large quantities of potassium lost in these cases indicate a process of "metabolic debridement" of necrotic tissue.

Henry and his associates (57) call attention to the depression of plasma potassium which follows the administration of insulin, and to a change in this response when it is elicited in an animal shortly after a severe scald of a hind leg. Whereas in the unburned animal the minimum potassium concentration was obtained at the end of 2 hr., in the burned animal it had dropped almost to the minimum in 30 min. and by 2 hr. was beginning to return toward normal. The interpretation of these data is uncertain.

On the basis of extensive studies, Moore and his co-workers (58, 59, 60), who have done yeoman's work in this field, divide convalescence from trauma into its four phases, namely, (*a*) the adrenergic corticoid phase; (*b*) the corticoid withdrawal phase; (*c*) the spontaneous anabolic phase; and (*d*) the fat gain phase.

That the adrenal cortical hormones have an effect on blood clotting has been shown by Garrett (61). Utilizing the *in vitro* heparin resistance clotting test, he found that there was a statistically significant reduction in the clotting delay in the first 48 hr. after operation, and that this occurred at about the same time as the fall in the eosinophil count.

Dutton (62) has also raised the possibility that the degree of clotting postoperatively is an indication of adrenocortical function. He has suggested

a clinical test utilizing adrenalin hydrochloride parenterally to determine preoperatively which patients are likely to show postoperative hypercoagulability.

The thyroid.—The relationship of the thyroid gland to trauma is still not clearly understood, but there is evidence that its activity may be increased following trauma. Hardy & Ravdin (63) demonstrated some increase in I^{131} uptake following trauma, although the increase was not striking. Goldenberg *et al.* (64) report definite increases in I^{131} uptake. Cope *et al.* (65), on the other hand, did not find the uptake increased after burns, although, following extensive burns, the basal metabolic rate was increased to from plus 30 to plus 60 per cent for as long as two months, and, after major surgery, the basal metabolic rate was increased for a few days. However, these authors do not believe that the thyroid plays a part in the rise in the basal metabolic rate. Goldenberg *et al.* (64) believe that the adrenocortical hormones counteract the thyroid hormones and re-establish equilibrium. They believe that the thyroid effect comes first and the adrenocortical reaction second. An imbalance results in nitrogen loss.

Dingwall *et al.* (45) report a case of thyroidectomy in a toxic patient in whom the eosinophils increased rather than fell, a fact that might fit in with a concept of antagonism between these hormones. Shipley & MacIntyre (66) found that the stress of major surgery was accompanied by a rise of the hormonal I^{131} of serum in three of nine patients. A similar effect was produced by the injection of thyroid stimulating hormone. Adrenocorticotropin did not influence the level. They believe that their results are compatible with the concept that acute stress causes a release of thyroid hormone from the gland. This concept might also explain the clinical observation of a thyroid storm-like state which we observed after adrenalectomy before large doses of cortisone were routine. The increased excretion of creatinine following trauma may well reflect the increased metabolic activity of the muscle mass (67).

Body Weight

That a certain degree of weight loss is to be expected after trauma has been emphasized by Moore (68), who pointed out that it usually averaged about 350 gm. per day. This normal trend in patients may be masked by fluid retention or exaggerated by abnormal fluid losses. As the body consumes and oxidizes its stores, it forms some "endogenous water" but not enough to affect the balances greatly. PaQuin (69) found a weight loss of from 2 to 6 gm./kg./day in fasting postoperative men after operative procedures. The determination of total body water gives a good index of the degree of adiposity since it varies inversely with the percentage of fat in a patient who is normally hydrated (70).

Fox *et al.* (71) point out the tendency for the local accumulation of albumin, sodium, and chloride in injured tissue with compensatory loss in

uninjured areas, and, in contrast, a local loss of potassium and a systemic increase in potassium ions. These changes help produce the local edema in injured areas, and plasma volume measurements show large losses of plasma from the vascular spaces.

Cellular and Enzymatic Reactions to Injury

Cameron (72), in a recent review of the tissue response to injury, concludes that only when the exudate contains specific antibodies against the invaders do we find convincing evidence for the view that inflammation is protective in function. Utilizing the granuloma pouch technique in the experimental animal, Selye (73) found that hydrocortisone inhibits the phlogistic effect of irritants without impeding their necrotizing action. He concluded that necrosis and inflammation are separate processes in the response to irritation.

Stewart *et al.* (74) found that in the dog, hepatic cells reacted to anoxic injury by an immediate and moderate loss of cellular potassium, with a tendency toward reversal when the normal circulation was re-established. The adrenocortical hormones did not seem to play a part in the potassium loss as was shown by using adrenalectomized animals. In the postoperative period, serum cholinesterase levels were found by Tonelli & Pesci (75) to be decreased approximately in proportion to the severity of the operative procedure. By the tenth postoperative day, the serum cholinesterase level had attained at least 90 per cent of its initial value in the majority of cases.

Baker (76) has summarized the previously published data indicating that the absorption of fat, sodium chloride, and glucose is reduced by adrenalectomy, and that there is a reduction in weight of the gastrointestinal mucosa after adrenalectomy. He demonstrated that hypophysectomy causes severe atrophy of the zymogenic cells of the stomach, pancreas and parotid gland, and that the adrenal gland plays a role in the secretions of these glands.

Judah & Spector (77) have reviewed some of the reactions of enzymes to injury. They discuss current knowledge encompassing the genetic, radiation, and toxic changes within various enzyme systems. Milch and his co-workers (78) found that plasma cholesterol was increased markedly in traumatized rabbits. They also found significant increases in the plasma concentration of the S_f 12–20 and S_f 20–100 classes of lipoproteins. They believe that tissue cells synthesize increased amounts of cholesterol as an integral part of the repair process.

Beck, Linkenheimer & Marraccini (79) studied the effects of several types of trauma on rat tissue nonprotein sulfhydryl. They found significant decreases in rat liver sulfhydryl following tumbling trauma, and in both liver and kidney of rats following severe scalding, though the blood nonprotein sulfhydryl concentrations were almost identical for control and tumbled rats. Following thermal trauma, some increase in the concentration of nonprotein sulfhydryl occurred in the blood paralleling the hemoconcentration.

Albaum & Milch (80) studied the adenosine triphosphate (ATP) levels in muscles removed from rabbits 18 hr. after trauma (cold, heat, and crush injury). Freezing led to a 90 per cent reduction in ATP content, but lesser degrees of cold did not produce a significant decrease. Heat and crush injuries produced a 50 per cent decrease under the conditions of the experiments of these authors. They pointed out that the ATP level in the tissue represents a balance between the energy made available during the breakdown of substrate and its utilization.

Roth (81) studied the incorporation of N^{15} into protein and P^{32} into nucleic acid in thermally injured rats. During the first 24 hr., the incorporation of N^{15} was depressed 10 per cent, but increased sharply during the succeeding two days. The incorporation of P^{32} into the tissue nucleic acid was greatly reduced after 24 hr. in liver and intestine but increased in kidney and spleen.

Green & Stoner (82) reiterate that the cardinal feature of shock from any injury, in any species, is a depression of energy production. After a comprehensive review of their own work in energy metabolism in shock due to various forms of injury, and the work of others, they conclude that little is really known of the biochemical mechanisms concerned.

Nutrition and Intermediary Metabolism

Levenson, Howard & Rosen (83) carried out detailed analyses of serial blood samples obtained from five severely wounded young soldiers. Analyses were carried out for nonprotein nitrogen, creatine plus creatinine, uric acid, other purines, urea, and, in addition, 19 individual amino acids which were quantitatively analyzed by ion exchange chromatography. Shock and renal failure were present in all five patients in varying degrees, and four of the five died. No plasma amino nitrogen level over 5.8 mg. per cent was found. Renal failure was persistent in four of the patients and, although plasma urea concentrations were as much as 30 times normal, total free plasma amino acid nitrogen levels were near normal. In those patients studied for periods extending from the day of injury to two weeks after injury, the plasma amino acids followed a pattern. At no time were all the amino acids depressed or elevated. Rather, they grouped themselves as follows: (*a*) glycine, histidine, threonine, proline, and glutamic acid stayed near normal; (*b*) leucine, isoleucine, lysine, valine, tyrosine, and alanine rose moderately during the first week and then fell; (*c*) phenylalanine, aspartic acid, and methionine also rose during the first week, but to a greater degree. Taurine bore little or no relation to the other amino acids. At times, it was very high. In two patients who became markedly malnourished, the total plasma amino nitrogen concentration fell to low levels.

In all plasmas analyzed, a heterogeneous amino conjugate was found. The amino acid composition of this conjugate varied from patient to patient, and in the same patient on different days. In general, those patients with the highest nonprotein nitrogen levels had the amino acid conjugates in greatest

concentration. In these cases, acid hydrolysis revealed maximum numbers of different constituent amino acids.

The use of the artificial kidney in three of the cases produced a notable reduction of all the small nitrogenous compounds in the plasma, with the exception of the amino acids whose total level generally remained unchanged. The plasma amino acid conjugates, however, behaved like a metabolic end product and, like urea, their level fell sharply after dialysis.

The rise in "undetermined nitrogen" after burns has been noted by the French and received attention in some detail in this country by the clinical studies of Walker (84) and by studies in animals by Rosenthal & McCarthy (85). The study by Levenson and his associates (83) represents a noteworthy advance in the study of the nonprotein nitrogen fractions in the serum following severe trauma.

Nutritional Aspects of Trauma

Blocker and his associates (86, 87) in a study of the nutritional status of severely burned patients note that low A/G ratios persist in spite of steadily rising serum protein levels. Electrophoretic data indicate that there is at first a low A/G ratio because of the loss of albumin from the circulatory system without appreciable changes in the globulin fractions; within one or two days the gamma globulin content increases considerably, and, although there is a simultaneous increase in albumin, the rise in gamma globulin is such that the A/G ratio again starts to fall. Experiments utilizing l-methionine labeled with radiosulfur 35 in normal and burned patients indicated that the nutritional defect following thermal trauma was a protein disequilibrium involving accelerated rates of both protein anabolism and protein catabolism, with the latter a much more prominent phenomenon. The rate of catabolism is so greatly increased that equilibrium is not established until the healing phase is approached.

Howard (88) reported studies of the absorption and metabolism of glucose following trauma. He stated that the blood sugar rose higher after the oral ingestion of 100 gm. of glucose in those patients with severe injuries than in those patients with minor injuries whose curves were in turn somewhat higher than those of normal controls. Insulin tolerance curves showed relative flattening following injury, particularly following severe injury, with a tendency of the curve to return toward normal with convalescence. Similar glucose tolerance curves were reported by Wolff and his associates (89) following thermal burns.

Hayes (90) calls attention to certain biochemical evidence of possible thiamine deficiency in convalescence from surgical operations. He observed elevation in blood levels of pyruvate and lactate following intravenous glucose, which he believed reflected a significant decrease in cocarboxylase, the prosthetic group for the enzyme decarboxylase and for which thiamine is the precursor. He stated that it appears that the convalescent requirements,

whether parenterally or orally given, are about 10 times those established as maintenance amounts for adults.

Cole, Schneewind & Canham (91) have published a review on the rôle of protein metabolism in surgery, which examines many facets of the interrelations between surgical trauma and protein nutrition. Payne & Krauel (92) call attention to shifts in fats as a result of thermal burns. They find lipids in the exudate from the burned surface and call attention to the appearance of lipids in lymph draining from the area of a burn in the first few hours. Much of this is in the form of phospholipids. Reduction in fat in the burned area was demonstrated by lipid analysis of normal and burned pigskin. The cholesterol concentration of lymph was noted to rise markedly also after burning, though the cholesterol apparently represented but a small fraction of the total lipid.

A study of the effect of the previous level of protein feeding on the metabolic response to injury and on wound healing was carried out at the Army Nutritional Laboratory by Calloway, Grossman, Bowman & Calhoun (93). High protein intakes resulted in higher urinary nitrogen excretion, higher liver nitrogen content, and a more sharply negative nitrogen balance immediately following the injury. There appeared to be no practical advantages in increasing an ordinary protein ration by 200 or 300 per cent.

Campbell, Sharp, Boyne & Cuthbertson (94) have published an interesting paper on cortisone and the metabolic response to injury. In addition to other observations, these authors found that the catabolic response to injury was absent in adrenalectomized animals able to maintain themselves with saline, but re-appeared when such animals were fed cortisone daily at a maintenance level. The test trauma was fracture.

Seifert, Lambrecht & Manck (95) studied 80 cases of cerebral damage associated with unconsciousness by means of the Widmark test, and 90 per cent of the cases showed an increase of the alkali reserve of the blood.

Autopsy Studies

A recent review of postmortem examinations in combat casualties was reported by Strawitz, Scully, Vickery & Howard (96). The commonest cause of death in this series of 35 individuals was irreversible shock. Other causes were more directly explainable on a mechanical basis, such as vital organ damage, uncontrolled hemorrhage, bronchial obstruction, cardiac arrest, traumatic coronary thrombosis, and subdural hematoma. The histologic studies did not appear to throw additional light on the mechanism of irreversible shock. Congestion of striated muscle was noted, particularly in casualties in which strenuous efforts at resuscitation had been carried out with whole blood and other fluids. Other morphologic changes listed in irreversible shock were: (*a*) petechial hemorrhages—serosal, mucosal (gastrointestinal); (*b*) dilatation and engorgement of vessels in the abdomen and thoracic viscera, the brain, and striated muscle; (*c*) pulmonary edema; (*d*) pulmonary

atelectasis, focal and diffuse; (*e*) dilatation of cardiac chambers with flabbiness of the myocardium; (*f*) renal tubular changes consistent with posttraumatic renal insufficiency (microscopic); (*g*) lipoid depletion—adrenal cortex cells (microscopic); (*h*) fatty vacuolation—heart muscle, liver, kidney (microscopic). These findings follow fairly closely those observed by and emphasized by Moon in 1937 (97).

The period reviewed has been one in which extensive investigative activity in the field of trauma has been reported. More attention has been devoted to the systemic and metabolic effects of trauma as compared with the local wound or injury than in any similar period. Space does not permit an exhaustive review, but we have endeavored to cover the main topics with emphasis on the American and English literature. It is hoped that the reader may at least be guided to suitable references from which he may then be able to explore a given field more thoroughly by cross references.

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LABORATORY AIDS TO DIAGNOSIS AND THERAPY[1]

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A plan to facilitate the adoption and standardization of a uniform procedure for estimation of hemoglobin is one of the outstanding accomplishments of the year [Cannan (1, 2)]. The technic to be made standard depends upon the formation of cynanmethemoglobin, one of the more stable compounds derived from hemoglobin [Crosby, Munn & Furth (3)]. The concentration of potassium cyanide used is low enough (52 mg. per l.) to allay concern about toxicity. A standard of reference in the form of a crystalline human hemoglobin prepared by the method of Drabkin is to be standardized by means of spectrophotometry and iron determinations in four master laboratories. A millimolar extinction coefficient of 11.5 at 540 mμ. of a solution of cyanmethemoglobin is defined as representing one milliatom of hemoglobin iron per l. The iron content of hemoglobin accepted as standard is 0.335 per cent. This corresponds to an equivalent weight of 16,700 per atom of iron or a molecular weight of 66,880 and an oxygen capacity of 1.34 ml. per g. of hemoglobin. The stability of the cyanmethemoglobin will permit distribution of certified solutions. These are to be given one year of field trial under the supervision of an ad hoc Panel on the Establishment of a Hemoglobin Standard of the Division of Medical Sciences, National Academy of Sciences, National Research Council. These proposals have been criticized somewhat by Sunderman *et al.* (192) who describe procedures suitable for hemoglobin standardization in the laboratory (193).

The use of copper-ammonium standards for photometric measurement of hemoglobin proposed by Drabkin (4) has been evaluated by Flood *et al.* (5). Variations in hemoglobin equivalence, apparently depending upon the purity of the copper sulfate and its hydration, led to the conclusion that this standard is not suitable for precise calibrations. However, in practice it serves well for use with the Klett-Summerson photocolorimeter, although not in spectrophotometers. It should now be replaced by the new standard cyanmethemoglobin solutions.

Ellerbrook & Davis (6) found that traces of copper in the solutions used for diluting blood previous to measurement of oxyhemoglobin absorbancy caused rapid fading and erroneous readings.

An improved micro-hematocrit method which eliminates error due to trapped plasma was described by Strumia, Sample & Hart (7).

Several previously unknown abnormal hemoglobins were identified during the past year. Hemoglobin E [Itano, Bergren & Sturgeon (8); Chernoff, Minnich & Chongchareonsuk (183)] migrated between S and C on paper at

[1] The survey of the literature in this review was completed in June 1955 but papers presented at the Third International Congress of Biochemistry in Brussels, August 1 to 5, have been included.

pH 8.6. Chernoff *et al.* (9) describe its occurrence in 35 Thais. Five of these had "pure" hemoglobin E disease, 14 had a combination of hemoglobin E disease and Mediterranean anemia, and 20 merely showed the E trait.

Hemoglobin G has been found by Edington & Lehman (10) in a West African. It migrated between A and S on paper at pH 8.6.

A hemoglobin migrating more slowly than A at pH 6.5 or 7.8, yet which has the same mobility as A at pH 8.6, was discovered by Battle & Lewis (11) in two members of a white family. Each showed chronic spherocytic anemia, mild jaundice, and splenomegaly.

Rapidly migrating hemoglobins, outdistancing A at pH 8.6, were identified in a Chinese family [Rigas, Koler & Osgood (12)] and in negroes [Jensen, Page & Rucknagel (13)]. Both groups proposed the designation H; however, it seems unlikely that they are the same.

It is not possible to review the papers describing interrelationships of the various hemoglobins. White & Beavan (14), Schwartz (15), and Singer (163) have summarized the current knowledge of human hemoglobins in review articles.

Electrophoretic separation of hemoglobins is more difficult than is separation of plasma proteins, and technics that serve for the latter may not be suitable for hemoglobin studies. Motulsky, Paul & Durrum (16) described the use of the Durrum "vertical strip" apparatus for this purpose. Their article includes many examples of different combinations encountered in patients. Goldberg (17) found that addition of sucrose to the buffer sharpened the separations when the compressed strip apparatus of Raymond (184) was used. Important modifications of the technic of using the Grassmann & Hannig (185) apparatus are required to enable separation of hemoglobins. These include application of pressure across the ends of the paper and narrowing the paper where it dips into the buffer to diminish buffer flow, the addition of glycerol to the buffer, and the use of freshly prepared or well preserved hemoglobin [Goldberg (18)].

According to Singer (163), paper electrophoresis at pH 8.6 in combination with the alkali denaturation test will enable identification of almost any of the abnormalities so far described. If the presence of D is suspected, solubility studies may be required. Occasionally, electrophoresis at a pH of 7.8 or 6.5 may be needed [Battle & Lewis (11)].

A new and promising approach to the identification of human hemoglobins involved the use of chromatography on Amberlite IRC 50 (XC 54) [Prims & Huisman (19)]. A simplified method employed flat Lucite cuvettes as containers for the column of resin. The various hemoglobins were resolved on the resin with the aid of sodium citrate buffer (0.15 M) at pH 6.5 and the bands photographed against the white background of the resin. A more quantitative method consisted of elution and photometric measurement of the eluates. Carbon monoxide derivatives were used. By this method, mixtures of hemoglobin A and F were readily resolved.

Amino Acids and Amines

Measurement of amino acid clearance may be necessary to distinguish between "overflow" and "renal" aminoacidurias [Dent (20); Dent & Walshe (21); and Harris (22)]. These articles provide excellent reviews of disturbances in amino acid metabolism. In the Fanconi syndrome, clearances of amino acids were increased and plasma amino acid concentrations remained within normal limits. In cystinurics when plasma concentrations of cystine were elevated by feeding cysteine, the renal clearance of cystine did not rise, as it did in normal controls, but remained unchanged at a rate approaching that of glomerular filtration [Dent, Heathcote & Joron (23); Dent, Senior & Walshe (24)]. According to Harris (22) the renal aminoacidurias include, in addition to cystinuria and the Fanconi syndrome, Wilson's disease, galactosemia, scurvy, rickets, lead poisoning, "Harts" syndrome (Dent (25)], and the syndrome of decreased ammonia production, increased excretion of organic acid, hydrophthalmos, and mental retardation described by Lowe, Terry & MacLachlan (26). Causes of overflow aminoacidurias include phenylketonuria and liver disease.

Lowry *et al.* (27) developed a spectrophotometric method for measurement of histamine in blood in amounts of 0.01 μg. and concentrations of 4×10^{-10}. They found 4.3 μg. per liter in human plasma. However, only 60 per cent of this amount was destroyed by histaminase.

Noradrenaline and adrenaline were measured in urine by a simplified fluorometric technic by Pekkarinen & Pitkänen (28). A huge increase in the excretion of these amines in the urine of a patient with a paraganglioma was observed (29).

Patients with paroxysmal flushing caused by malignant carcinoid had elevated concentrations of 5-hydroxytryptamine (serotonin) in blood [Pernow & Waldenström (30)]. Acetone extracts of blood serum and urine were assayed with the aid of segments of rat intestine. The presence of increased concentrations of this substance provided a diagnostic sign comparable in value to the measurement of acid phosphatase in carcinoma of the prostate, adrenaline and noradrenaline in pheochromocytoma, or of gonadotropin in chorionic epithelioma.

Methods for estimation of serotonin in urine more specific than those previously available have been proposed by Sheperd, West & Erspamer (31), who used paper chromatography, and by Bumpus & Page (32) who separated three peaks of pressor activity corresponding to bufotenin, N-methyl serotonin, and serotonin, by adsorption of urine on alumina. Clark, Weissbach & Udenfriend (33) described the preparation and properties of an enzyme, 5-hydroxytryptophan decarboxylase, which may aid in measurement of 5-hydroxytryptamine concentrations of body fluids. A relatively simple chromatographic method for tryptamine and hydroxytryptamine was described by Rodnight (34).

Diagnosis of Pancreatic Disease

Elman (35) cautioned against the uncritical acceptance of elevated serum amylase activities as diagnostic of acute pancreatitis. He mentioned administration of opiates, anuria, strangulation of the intestine, perforation of a peptic ulcer and laboratory errors as other causes of a high serum amylase, or its being so reported. In these clinical conditions the rise in amylase activity ordinarily was only moderate (2 to 5 times normal) as compared with the much greater elevations (10 to 30 times normal) occurring in acute pancreatitis. However, Bogoch, Roth & Bockus (36) found that morphine caused serum amylase to rise in three of 41 patients to the range of values observed in acute pancreatitis. Five additional patients showed less marked increases. In acute alcoholism, moderately elevated amylase activities were observed in six of 51 patients by Culotta & Howard (37). Perryman & Hoerr (38) found elevated serum amylase activities to occur frequently after operations, especially if the common duct had been manipulated or after gastric resection.

The effectiveness of the secretin test has been compared with that of the plasma antithrombin titer, the serum amylase concentration, and serum mucoprotein level by Dreiling, Greenspan & Sanders (39) in a group consisting mainly of patients with chronic pancreatic disease though some had malignant disease of the pancreas or acute pancreatitis. No definite correlation was observed. Nearly all of the secretin tests were abnormal. Antithrombin titer was graded second in usefulness, and was most helpful when the secretin test could not be performed. Serum mucoprotein concentrations were influenced by factors other than pancreatic disease. Serum amylase was least often abnormal and contributed no useful information except in acute pancreatitis.

A rapid turbidimetric method for measuring serum amylase activities was described by Peralta & Reinhold (40).

Calcium and Phosphate

Hyperparathyroidism is not a rare disease [Milne (41)] and its diagnosis at times may be troublesome. Schaaf & Kyle (42) measured the reabsorption of phosphate in hyperparathyroid patients by carrying out simultaneous creatinine and phosphate clearances. Phosphate reabsorption in healthy controls averaged 91.3 per cent, with a standard deviation of 3.3 per cent. Three patients with primary hyperparathyroidism reabsorbed 50, 60, and 65 per cent. Removal of a parathyroid adenoma from one was followed by a rise in phosphate reabsorption. The method cannot be used in the presence of severe kidney damage. McGeown (43) investigated a group of patients with recurrent urinary calculi by means of phosphate clearances. However, the clearances did not differ from those of normal subjects. She also found low phosphate clearance in a patient with parathyroid adenoma.

Anderson *et al.* (44) found that the hypercalcemia of sarcoidosis was corrected by the administration of cortisone. The hypercalcemia of a hyper-

parathyroid patient remained unaffected by similar treatment. They suggested that cortisone might be used to differentiate the hypercalcemia of sarcoidosis from that due to other causes.

A syndrome of hypercalcemia, hyperphosphatemia, hyperazotemia, hypercalcuria, osteosclerosis, and dwarfism was described by Fanconi (45). McCance, Morrison, and Dent (46) observed phosphoethanolamine in the urine of an infant suffering from hypophosphatasia, a syndrome including rachitic bone changes, hypercalcemia, and low alkaline phosphatase activity in the serum.

Electrophoresis and Proteins

Several new approaches to the separation of substances by electromigration have been proposed. Kolin (47) combined a pH gradient with an electrical field and in this way caused ampholytes to converge toward points at which the pH was isoelectric. Brakke (48) produced density gradients by adding glucose solutions of decreasing concentrations to U tubes. Electroosmosis was eliminated as was diffusion and adsorption. Sorof & Ott (49) use sucrose as a barrier to convection in preparative electrophoresis.

Flodin & Porath (50) and Carlson (51) found the use of vertical columns of starch for zone electrophoresis advantageous. The high voltage vertical apparatus for zone electrophoresis on paper described several years ago by Michl (52) has been applied to the separation of amino acids, peptides, and many other components of blood serum by Heilmeyer *et al.* (53). A very large number of substances were differentiated in normal and abnormal sera. Noller (54) used thread for electrophoretic separation of very minute amounts of material.

McDonald (55) and Durrum (56) and Enselme & Dreyfus (57) reviewed the applications of zone electrophoresis in their respective books and provided helpful bibliographies. Verschure & Boom (58) discussed its clinical application. Flynn (59) assembled 42 different electrophoretic patterns illustrating major changes occurring in a variety of clinical conditions.

Changes in serum and urine proteins occurring in the nephrotic syndrome were described by Hardwiche (60) and Stickler, Burke & McKenzie (61). Hardwiche found in some patients (but not in the entire group) a relationship between loss of protein in urine and a rise in alpha$_2$, beta$_1$, and fibrinogen and fall in albumin. Following myocardial infarction the patients studied by Kaufman & Majerus (62) had elevated alpha$_2$ globulins for about one month owing to the presence of glycoprotein in increased concentrations. The appearance of a new zone between alpha$_2$ and beta was noted. A rise in beta globulin was less persistent. Linko & Waris (186) found fair correlation between alpha$_2$ globulin concentrations and sedimentation rates in myocardial infarction. Plasma mucoprotein concentrations did not increase more rapidly or more frequently than did the erythrocyte sedimentation rate in such patients (187). A study of serum proteins in myeloid leukemia by Andersch, Sacks & Barbusca (63) showed that a rise in alpha$_2$ globulin concentration

was the most frequent change occuring in 16 of 21 patients studied. Albumin concentrations fell in 13 of 20. Rises in alpha$_1$ and gamma were less frequent. Wall & Sun (64) reported that an excellent correlation existed between clinical activity of Hodgkin's disease and related lymphomas and elevation of alpha$_2$ globulin concentration.

Multiple sclerosis was accompanied by increases in all of the principal serum globulin components. In the cerebrospinal fluid, lowered albumin and elevated beta and gamma globulin concentrations were noteworthy [Roboz *et al.* (65)]. Manze & Armand (66) studied serum proteins of lepers and found lowered albumin and elevation of all globulin fractions by roughly 1.5 times over the normal.

A lowered alpha globulin was observed within three days of the onset of viral hepatitis [Schaffner, Scherbel & Lyttle (67)]. This fraction fell in the remaining patients within the first week. The lowering of the alpha$_1$ globulin persisted longer than did the elevation of gamma globulin. Minimal alpha$_1$ values were observed as late as the fourth week after onset in six of 13 patients. Such changes were to be expected in view of Miller's (68) finding that mucoproteins are elaborated in the liver.[2]

Greenspan (69) surveyed the changes occurring in serum mucoprotein concentrations in disease. Elevated values occurred in inflammatory and neoplastic diseases and following tissue injury caused by thrombosis or trauma. Low levels were characteristic in patients with viral hepatitis, Addison's disease, or panhypopituitary disease. Keyser & Heppleston (70) demonstrated that the acute inflammation produced by intraperitoneal injection of silica was closely paralleled by a rise in serum polysaccharide, whereas fibrosis and macrophage response became prominent at a time of falling concentrations of these mucoprotein components. Kushner and co-workers (71) reported that typhoid vaccine, corticotrophin, surgical procedures, and parathyroid extract cause the mucoprotein of serum to increase promptly.

Opinions differed concerning the value of measurement of serum mucoprotein concentrations. Rhees, Ellerbrook & Lippincott (72) found elevated levels in 49 per cent of patients with malignant disease. However, 32 per cent of those with miscellaneous diseases also had elevated levels. Mandel, Gorsuch & Cooper (73) found seromucoid (mucoprotein) measurements to have shortcomings as an aid to the diagnosis of patients with jaundice and hepatomegaly or both. However, the lower limit of normal provided a useful, although empirical, dividing line between obstructive and parenchymal jaundice. Kushner *et al.* (74) agreed that, for diagnosis of specific disease, its value was limited. On the other hand they found it valuable for (*a*) excluding malignant disease, (*b*) the differential diagnosis of jaundice, and (*c*) for fol-

[2] Mucoproteins (seromucoids) of serum are rich in polysaccharide. At pH 8.6 they migrate electrophoretically, at least in large part, as alpha globulins. Thus measurements of serum polysaccharide, mucoprotein, or alpha globulin concentrations may provide estimates of the same fundamental changes in composition.

lowing the activity of chronic infectious hepatic and rheumatic disease.

Further proof that the mucoproteins of serum have an important rôle in governing the response to such reagents as colloidal gold, thymol-barbital, and zinc sulfate, when these are used for testing serum, was provided by Anderson, Lockey & Maclagan (75). In experiments in which they added to serum increasing amounts of purified mucoproteins, colloidal gold reactions of abnormal type occurred only when the mucoprotein was less than 500 mg. per 100 ml. Thymol and zinc turbidity readings became less abnormal as mucroprotein was increased and, when sufficient mucoprotein was present, became negative. A general correlation between mucoprotein and sedimentation rate also was noted. Shetlar and co-workers (76) observed that C-reactive protein titers of serum varied with mucoprotein concentrations of serum.

Measurement of the protein-bound polysaccharide of serum offers certain advantages over other methods of estimating mucoproteins and glycoproteins. Bjornesjo (188) described a simple method for applying the anthrone reagent for this purpose and correcting for interference by tryptophan. A second paper (189) evaluated the staining of protein-bound serum polysaccharides.

Stary & Ugur (77) reported that a glycoprotein prepared from beef serum migrated as two peaks with the mobility of albumin in the Tiselius moving boundary apparatus. On paper, it migrated as alpha globulin either in the presence or absence of albumin. They attributed this to a specific retardation on paper.

Electrophoretic study of urine proteins aided the identification of abnormal proteins in urine, especially those occurring in multiple myeloma. Osserman & Lawlor (78) found, in a group of 35 patients suffering from multiple myeloma, that seven had abnormal urine proteins, as shown by zone electrophoresis, when the serum protein pattern showed no changes that were diagnostic. In 33 of the 35, either serum or urine showed a characteristic abnormality. Abnormal urine proteins showed evidence of the homogeneity typified by the abnormal serum proteins in multiple myeloma. Latham *et al.* (79) studied the urine proteins of persons with orthostatic albuminuria by means of zone electrophoresis and found no change during orthostasis other than dilution of all fractions. The application of zone electrophoresis to the study of urine proteins was evaluated by Wolvius & Verschure (80). They found it to be reliable if the protein concentration exceeded 1.5 per cent. Wunderly & Caspari (81) made an electrophoretic study of urine proteins in various types of kidney disease.

Continued investigation of agammaglobulinemia has revealed that adults as well as children may suffer from this condition [Sanford, Favour & Tribeman (82); Grant & Wallace (83); Zimmerman, Hall & Heller (84); Gras, Latorre & Gamissares (85); Prasad & Koza (86); Young & Wolfson (87); Collins & Dudley (88); Wall & Saslaw (89); Rohn, Behnke & Bond (90); Seltzer, Baron & Toporek (91)]. It appears that the acquired type may be

more prevalent, by far, than the familial. Both lymphopenic and nonlymphopenic familial types exist [Young & Wolfson (87).] Elevated concentrations of gamma globulin were observed in relatives of one of their patients. Absence of plasma cells was noted by Zimmerman *et al.* (84) and Collins & Dudley (88). A sprue-like syndrome has been described in several patients [Sanford *et al.* (82); Wall & Saslaw (99); Rohn *et al.* (90)], although a history of repeated or persistent infectious disease is the more common background. Virtual absence of gamma globulin may occur in patients with lymphomas and myelomas [Rohn *et al.* (90); Young & Wolfson (87)].

Porter (92) described a method for fractionation of gamma globulin by means of partition chromatography. Horeski & Smetana (93) discovered that rivanol (2-ethoxy-6,9-diaminoacridine) in 0.4 per cent solution (3 parts) quantitatively precipitated all proteins in serum (1 part) except gamma globulin. Gamma globulin so prepared was undenatured and contained only 3 per cent of beta globulin as an impurity. Chromatographic separation of serum proteins by means of Dowex 2 (in Cl form) was described by Boman (94), and Fowell (95); Jacox (96) and Saifer & Newhouse (97) published methods for analysis of fibrinogen.

Lipoproteins and Lipides

Serum lipides staining with Sudan black after electrophoretic separation on paper included two or three zones in the alpha globulin region, a "pre-beta" band moving ahead of beta (in about one-third), a strong beta zone, and a trail of lipide extending from the beta zone to the origin [Dangerfield & Smith (98)]. The pre-beta band stained strongly in sera of nephrotics and had a different hue. It contained little cholesterol. Patients with coronary thrombosis also tended to have intense pre-beta bands, 57 per cent showing this peculiarity as compared with 18 per cent of normals (100).

Jencks & Durrum (101) improved the procedure for staining lipides on paper. Their method used oil red O in aqueous solution. They criticized the use of 50 per cent ethanol, which had been widely adopted for removing surplus stain, on the grounds that it also removed some lipides.

In a summary of studies on lipoproteins made with the aid of the analytical ultracentrifuge, Gofman *et al.* (102) stated that lipoprotein analyses made possible differentiation of poorly defined aberrations of lipide metabolism far more effectively than did the nebulous clinical criteria previously used. Rubin (103) found lowered $S_{f_{0-12}}$ lipoprotein concentrations in infectious mononucleosis. This contrasted with viral hepatitis in which all lipide fractions tended to rise. Frazer (104) reviewed the topic of lipoproteins, and Carlson (51) described their electrophoretic separation on a vertical column of starch.

Sperry & Brand (105) described a method for isolation and accurate measurement of total lipide in blood, thus supplying a need that had existed for a long time.

Liver Disease

Blood ammonia.—An elevated ammonia concentration in blood is one of the factors contributing to the syndrome of hepatic coma [Gabuzda, Phillips & Davidson (107)]. However, an appraisal of the significance of blood ammonia in liver disease is difficult because of the variety of figures reported from different laboratories. The differences are mainly the result of the rapid release of ammonia by blood after it is shed, and until an effective method is discovered for preventing this change, accuracy will remain poor. Conway (108) stated that liberation of ammonia was prevented by collecting blood under CO_2 or alveolar air; however, Phear, Sherlock & Summerskill (109) (and the writer) failed to confirm this. Chilling the blood aids in preventing the rise in blood ammonia, and the most acceptable values are those obtained by starting analysis of iced samples with minimal delay. Conway (108) and Conway & Cooke (110) extrapolated to zero time the results of a series of analyses and found the ammonia in the blood estimated in this way to be nil. Phear *et al.* (109) started their analyses three minutes after blood was collected. They stated that values so obtained were more reliable and representative than those found when the time was not rigidly regulated.

A new microdiffusion method for blood ammonia has been developed by Seligson [see Simmons & Gentzkow (111)]. Transfer of ammonia from blood to absorbent is more efficient than in the Conway method.

The elevation of blood ammonia concentrations in cirrhosis depended mainly upon the extent that blood was shunted around the liver [Mann and co-workers (112); White *et al.* (113); Phear *et al.* (109)]. Liver damage caused by carbon tetrachloride or hepatitis had little effect [Mann *et al.* (112); Traeger *et al.* (114); White *et al.* (113); Phear (109)]. The latter concluded that blood ammonia measurements were not useful for estimating long term prognosis of cirrhosis. Moreover, they considered them impractical for use as a measure of liver function, mainly because of uncertainties connected with the measurement, and unnecessary for diagnosis of hepatic coma which could be recognized readily from the clinical picture of personality change and tremor.

Of patients in hepatic coma, 80 per cent had elevated blood ammonia concentrations [Mann *et al.* (112)]. The Bessmans (115) found a close correlation between ammonia level and clinical state, and Riddell & McDermott (116) used blood ammonia measurements to follow the response to infusions of sodium glutamate. On the other hand, Singh, Barclay & Cooke (117) could not correlate the clinical state of patients in hepatic coma with their ammoniam levels, and Traeger *et al.* (114) found the correlation not sufficiently close to establish a causal relationship. However, an elevated cerebrospinal fluid ammonia (over 105 μg. per 100 ml.) was associated with mental disturbances in each of five patients [McDermott, Adams & Riddell (118)].

Several groups have tested the response of patients with liver disease to

ingestion of ammonium chloride [Traeger *et al.* (114) and Phear *et al.* (109)]. White *et al.* (113) gave 3 gm. by mouth and found elevated blood ammonia concentrations in patients with severe liver disease. However, two patients with obstructive jaundice and one with Chiari's syndrome also responded with high values.

No definitive statement may be made about the value of blood ammonia measurements at this time. Even with methods as imperfect as those used in the past, useful information can be obtained about disturbances of the liver and portal system provided a standardized technic is used. Postoperative care of patients following portacaval shunt operations probably could be made more effective if blood ammonia concentrations were known, and diet and other factors regulated accordingly. In the study of mental disturbances, also, measurement of ammonia concentrations in the body fluids may provide helpful clues [Havens & Child (119)].

Measurement of hepatic blood flow.—The rate of disappearance of radioactive colloidal gold from the circulation has been used for measurement of blood flow through the liver [Vetter, Falkner & Neumayr (120)]. Markedly decreased volumes of flow were measured in patients with cirrhosis.

Detection of carriers of viral hepatitis.—Some persons whose blood transmits viral hepatitis show signs of subclinical liver disease. These include abnormalities in hepatic tests [Neefe *et al.* (121); Stokes *et al.* (122)]. The possibility that this finding might be put to practical use was evaluated by Fitch and co-workers (123) who examined over 3600 blood donors by means of a group of hepatic tests. Viral hepatitis was detected in five recipients, and in each instance a donor had abnormal hepatic tests. The thymol turbidity [Maclagan (124)] and zinc sulfate turbidity [Kunkel (125)] were the tests most frequently abnormal in carriers of the hepatitis agent [Neefe *et al.* (121)]. Problems related to the evaluation of large numbers of blood donors by means of chemical tests were discussed by Reinhold (126).

Turbidity and flocculation tests.—The accurate measurement of turbid suspensions formed in the thymol turbidity test of Maclagan (124) is difficult. Visual comparison with turbidity standards of various types gives only an approximation, at best. Photometric measurements by means of photocolorimeters or spectrophotometers are more precise but the results, especially of thymol turbidity readings, may be quite different if measured in different instruments. Reinhold (127) described the preparation and standardization of colloidal glass suspensions that resembled in their optical properties the turbid suspensions formed in the thymol and zinc turbidity tests. Use of such standards decreased but did not eliminate inaccuracies in readings due to the instrument. The main cause of aberrations was the presence of high concentrations of fat in serum. Therefore, if the thymol test is used for examining nonfasting persons, for example blood donors, it is important to take into account the possible effects of lactescence [See Reinhold (126)].

Reinhold, Rawnsley & Yonan (99) found that zinc sulfate turbidity readings ("gamma globulin") of the sera of healthy negroes averaged 50 per cent higher than did those of whites.

Greenspan (128) described a new test, the acid-precipitable globulin turbidity (APG), which measures the alpha$_2$ plus beta globulin. Elevated readings were typical in biliary obstruction, especially if caused by malignancy, and in inflammatory disease of the biliary tract. On the other hand, low readings were usual in cirrhosis. Patients suffering from hepatitis gave results within the limits found for normal controls (148).

Bile pigments.—Billing (130) has described a chromatographic method for determination of three bile pigments in serum. This is similar to the method of reverse phase chromatography on siliconized kieselguhr which Cole & Lathe (131) used to establish the presence of several bile pigments (bilirubin and the two "polar" pigments I and II) in serum and in bile. Values for the total "polar" pigment, which correspond to the direct-reacting bilirubin, agreed more nearly with the results obtained by the Malloy & Evelyn (132) method for direct bilirubin, in which readings were made at 30 min., than with those found by the Ducci & Watson (133) method in which readings are made at 1 min. The latter measured only two-thirds of the polar pigment and depended more upon the total bilirubin. In a second paper, Billing (134) reported that the concentration of Pigment I in the sera of patients with hepatitis or biliary obstruction was increased to a greater extent proportionately than Pigment II or bilirubin. She postulated that the conversion of I to II was impaired.

Cole, Lathe & Billing (135) found that the maximum absorption of the polar pigments was at 419 mμ, as compared with 454 mμ for bilirubin. The absorption spectrum of the pigment in the serum of erythroblastotic infants was found by Boggs & Abelson (136) and Waters, Richert & Rawson (190) to have a peak in the region of 415 to 420 mμ in addition to that at 450 to 460 mμ observed in normal infants and characteristic of bilirubin. The 415 to 420 mμ peak has been attributed to products of hemolysis; however, the spectra of methemalbumin, oxyhemoglobin, and methemoglobin have maxima elsewhere. The coincidence of this peak in serum with that of the polar bile pigments suggests that the latter may contribute to the altered absorption spectrum of erythroblastosis.

According to Boggs & Abelson, the intensity of absorption in the region of 415 mμ is related to the severity of the disturbance in metabolism in erythroblastosis, and may be used in evaluating the need for exchange transfusion. Attempts by Claireaux, Cole & Lathe (137) to establish the nature of the pigment of kernicterus by chromatography and spectrophotometry provided no definitive answer because of interference by lipide, although the evidence pointed to bilirubin as the pigment of the icteric brain. However, Vogel (138) found the maximum absorption of kernicterus pigment to be at 425 mμ, and believed it to be mesobilirubin. Day (139) reported that biliru-

bin inhibited brain respiration *in vitro* and believed it to be the injurious agent. Review of these findings in the light of the newer knowledge of the bile pigments appears to be worth while.

A method for separation of bilirubin, mesobilirubin and urobilin pigments on paper was described by Stich, Kehl & Walter (140). Talafant (141) used paper electrophoresis to study direct and indirect bilirubins and Bollman & Mendez (142) used column chromatography. The quantitative spectrophotometric measurement of bilirubin and hemoglobin concentrations in plasma was described by Shinowara (143).

Electrophoresis of human fistula bile by Verschure (144) produced patterns on paper that included two bile pigments and two proteins. The more rapidly moving of the proteins had a mobility similar to that of serum albumin. In gall bladder bile, however, the various components tended to merge into a single zone which took up both protein and lipide stains.

Barrows, Hunter & Banker (106) found that oxyhemoglobin was the first pigment to appear in cerebrospinal fluid following subarachnoid, ventricular, or subdural hemorrhage. Bilirubin appeared after two or three days, increased as hemoglobin decreased, and persisted for two or three weeks. Bilirubin also appeared when flow of spinal fluid was obstructed and this the authors attributed to transudation. Methemoglobin formed when red cells were confined to a closed space, e.g. subdural hematoma. Berman, Lapham & Pastore (145) demonstrated that xanthochromia was detectable in cerebrospinal fluid when the bilirubin concentration exceeded 0.05 mg. per 100 ml.

Subclinical icterus was discovered in a significant number of patients in whom it might have been overlooked if routine tests for bilirubin in urine had not been done by means of a sensitive method [Shutkin & Caine (146)].

Chalmers *et al.* (147) reported that the action of adrenocorticotrophin on serum bilirubin varied in jaundice of differing etiologies. In four of nine patients with biliary obstruction, bilirubin concentrations decreased. Patients with cholangiolitic cirrhosis, congenital spherocytic jaundice, and constitutional hyperbilirubinemia also reponded to ACTH with a fall in bilirubin concentrations. Increased urobilinogen output in feces resulted in some patients, but in others bilirubin was removed by an unidentified pathway.

A syndrome of chronic idiopathic jaundice in which the liver cells obtained at biopsy contained considerable amounts of coarsely granular, brown pigment was described by Dubin & Johnson (148, 149).

Zieve & Hill (196) applied statistical technics for evaluating multivariate data to the appraisal of the relative effectiveness of liver function tests in cirrhosis, and Zieve, Hill & Hanson have done the same for viral hepatitis (197). In cirrhosis, the sulfobromophthalein test was most effective in differentiating between normal persons and patients with cirrhosis. Galactose tolerance, hippuric acid excretion, zinc turbidity, urinary coproporphyrin, and per cent of cholesterol esterified in serum were approximately three-fourths to two-fifths as effective. Urinary urobilinogen, thymol turbidity, and

serum bilirubin contributed least. Four of the tests studied—sulfobromophthalein, zinc turbidity, hippuric acid, and urinary coproporphyrin excretion—contributed virtually as much information as the entire group of nine. A cirrhosis abnormality score (CAS) was derived by combining the results of the four significant tests. The discriminative effectiveness of the combination was superior to that of sulfobromophthalein alone.

A study of viral hepatitis led to similar findings. Urinary coproporphyrin excretion ranked close to sulfobromophthalein in effectiveness and the thymol turbidity test was assigned a higher position than in cirrhosis. A hepatitis abnormality score based on the same four tests as the CAS was far more effective than any single test or pair of tests.

The usefulness of various hepatic tests for the study of patients suffering from metastatic cancer of the liver was evaluated by Simons (150). Alkaline phosphatase activity of the serum was elevated in all such patients who were jaundiced, and in roughly two out of three who were not. The ammonium sulfate turbidity also was abnormal in two-thirds, whereas the thymol turbidity and cephalin cholesterol flocculation were less frequently abnormal. An increased incidence of abnormal thymol turbidity when extrahepatic ducts were obstructed was surprisingly different from the usual experience. Brem (151) studied the use of hepatic tests for diagnosis of amebic abscesses of the liver. Seven of eight patients had some elevation of alkaline phosphatase in serum and in five this was significant. Abnormal retention of sulfobromophthalein occurred in half. Fewer than half showed changes in albumin or total globulin of serum or in flocculation tests.

Conclusive evidence of involvement of the liver in lupus erythematosus was obtained in about half of a group of 25 patients studied by Kofman, Johnson & Zimmerman (152). Actually thymol turbidity was abnormal in all patients. Walsh, Humoller & Zimmerman (153), in a study of multiple myeloma, found that only three of 20 patients had abnormal thymol turbidities, despite hyperglobulinemia in most. They concluded that an elevated thymol turbidity read in a patient with hyperglobulinemia was opposed to a diagnosis of multiple myeloma. In macroglobulinemia, thymol turbidity readings were abnormal [Waldenström (191)]. Dolin & Switzer (154) reported the occurrence of abnormal flocculation tests in multiple sclerosis. However, sulfobromophthalein, esterified cholesterol, and phosphatase measurements gave results within normal limits.

Patients who became jaundiced following therapy with chlorpromazine (Thorazine) had elevated alkaline phosphatase activities, elevated serum cholesterol concentrations, and negative flocculation tests [Zatuchni & Miller (155); Loftus and co-workers (156)]. Zatuchni & Miller found that the "Shay index," however, was less than 7.5. This index is calculated as the ratio of phosphatase activity in Bodansky units to mg. of cholesterol per 100 ml. of serum. Shay (157) found values greater than 7.5 in in the presence of extrahepatic obstruction and less than 7.5 in cholangiolitic hepatitits or in the inspissated bile syndrome. Chlorpromazine apparently induces the

latter and caution is required before surgery is employed in the mistaken belief that high phosphatase activity, acholic feces, and other signs of biliary obstruction warrant surgical intervention.

Gellis & Hsia (158) reviewed the problem presented by the study of liver function in childhood. Jones (159) listed laboratory findings that may be used to confirm clinical evidence of deterioration of hepatic function. These included an abrupt or steady rise in serum bilirubin, an abrupt rise in leucocyte count, a steady fall in serum albumin, a steady fall in serum cholinesterase, and an abrupt or steady fall in prothrombin.

Enzyme Activities of Body Fluids

LaDue, Wróblewski & Karmen (160) reported the occurrence of a striking rise in glutamic-oxalacetic transaminase activity in sera following acute myocardial infarction. The activity also rose in a number of other conditions including hepatitis, lymphomatous disease, leukemia, and rhabdomyosarcoma [Karmen, Wróblewski & LaDue (161)]. Methods for measuring transaminase activity are described in this paper. Destruction of liver tissue produced by carbon tetrachloride caused the activity of the serum transaminase to rise 500 to 1000 fold [Wróblewski & LaDue (162)]. High values occurred in hepatitis and in neoplastic disease of the liver, lesser elevations in cholangitis, and variable values in patients with cirrhosis. Serum transaminase activities of the latter tended to vary with the activity of the disease.

Serum aldolase activity was elevated in acute hepatitis, whereas it remained within normal limits or increased slightly in biliary obstruction [Bruns & Puls (164); Sibley & Fleisher (165)]. In serum of patients suffering from progressive muscular dystrophy high values also were found by Dreyfus, Schapira & Schapira (166) and Jacob & Neuhaus (167). The former found that the serum aldolase is not elevated in atrophies of nervous origin. Cook & Dounce (168) and Beck (169) have described and modified the method for serum aldolase.

The phosphohexose isomerase activity of serum was generally increased in patients with bone or liver tumors [Bodansky, Gershten & Wilson (170)]. Bruns & Jacob (171) found marked increases in acute viral hepatitis. Bodansky & Calitri (172) and Bruns & Hinsberg (173) have described methods for measurement of this enzyme in serum.

Walker *et al.* (174) concluded that when a beta-glycerophosphate substrate for serum acid phosphatase was used, increased activities occurred only when cancer of the prostate existed. Phenyl phosphate substrates were less specific. Hastrup & Videback (175) found a markedly elevated value when the serum of a child with Niemann-Pick disease was tested by means of phenyl phosphate. No increase in activity was demonstrated with glycerophosphate. Acid phosphatase activity was never elevated in women (174).

Sugars

A study of galactosemia by Schwarz and co-workers (176) showed that galactose-1-phosphate accumulated in large amounts in the erythrocytes of

galactosemic infants when these were exposed to galactose, whereas only small amounts were found in similar circumstances in erythrocytes from normal infants. Inorganic phosphate of plasma was lowered to a much greater extent following galactose administration in galactosemic infants than after glucose. This and other evidence supported the belief that conversion of galactose-1-phosphate to glucose-1-phosphate by galactowaldenase was impaired. In addition, this work demonstrated that the defect involved not only the liver but also other tissues.

Another defect of sugar metabolism, characterized by the presence of large amounts of sucrose in the urine, was described by Moncrieff & Wilkinson (177). Clinically it was manifested by marasmus, retarded mental development, and hiatus hernia, possibly congenital. Flynn (178) described two additional cases of essential pentosuria, a discovery aided by an extensive use of paper chromatography for study of urine specimens that showed evidence of reducing sugars. Isherwood (179) has reviewed the chromatography of sugars.

Roe (180) modified the method for measurement of blood sugar concentrations by means of anthrone. Addition of urea to a premixed reagent avoided some of the difficulties encountered with existing anthrone methods. Cerebrospinal fluid sugar could be determined without removal of protein. A quick and simple method for blood sugar in which dinitrosalicylic acid is used both for removal of proteins and reagent was developed by Lee (181). Bowman & Enterline (182) found that blood sugar was preserved well for 96 hr. by 10 mg. of sodium fluoride and 1 mg. of thymol per ml. Beyond this time the preservation was not satisfactory.

The increasing importance of clinical chemistry is demonstrated by the appearance of the first issue of the bimonthly journal *Clinical Chemistry* (194) in January, and by the announcement of a second journal, *Clinica Chimica Acta* (195), with plans to begin publication in 1956.

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TOXICOLOGIC ASPECTS OF OCCUPATIONAL HAZARDS[1]

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Within very recent years control of industrial hazards in the United States has become an integral part of plant operation. If the common industrial materials such as heavy metals and solvents still prove troublesome here and there, certainly it is the fault of application rather than the means of prevention, for these are now well defined in most instances. The accent is indeed on prevention; thoughts are being directed to tests of pretoxicosis rather than of injury. Considerations of comfort, rather than merely health, are being woven into the threshold limits of industrial exposure. The concept that the "total" man should be considered has brought into the fold many fields of study that have never gained consideration before. Toxicology has played no small role in the broadening of these concepts. Serious attention is being given to what were formerly fringe endeavors: psychology, psychiatry, effects of radiations, heat, light, vibration, noise, fatigue, color, and the design of machines fitted to the comfort of man. These enlarged and foresighted concepts have been recognized in the recent change of name from industrial health to occupational health, and have served to expand the realm of toxicologic activity. For the same reason, the number of fields that might be included in a review of this type is so large as not to permit the inclusion of all. Prominent among the topics omitted are discussions on occupational dermatoses, toxicology relating to pesticides, plastics, water quality, food, drugs and cosmetics, and methods of sampling and analyzing air-borne constituents.

A few volumes (1a) have been added to the toxicologic literature in the past two years: *Toxicology of Industrial Organic Solvents*, by E. Browning; *Aviation Toxicology*, by the Aero Medical Association; *The Halogenated Hydrocarbons, Their Toxicity and Potential Dangers*, by W. von Oettingen. A few limited reviews on toxicology have appeared within the year; the one by Goldblatt on "Research in Industrial Health in the Chemical Industry" (1b) expresses a decidedly English point of view. Also in England there appeared a critical review of experimental methods in determining chronic toxicity by Barnes & Denz (2). An incisive address by Seevers titled "Perspective vs. Caprice in Evaluating Toxicity of Chemicals in Man" (3) deserves attention. The Manufacturing Chemists' Assn., long a leader in the field of labeling dangerous chemicals, has published a third revision of its manual L-1, "Warning Labels;" New Jersey has recently developed a state code for labeling based on these recommendations. The Subcommittee on

[1] The survey of literature pertaining to this review was completed in July, 1955.

Toxicology of the National Research Council is planning to establish a toxicologic center where information may be obtained; presently, limited toxicologic information is obtainable from the Chemical Biological Coordination Center, Washington, D. C. The Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists has been active in adding many new chemicals yearly to the original list. A series of Hygienic Guides on Hazardous Industrial Chemicals, useful for plant supervisors, is being prepared by the American Industrial Hygiene Association, and an Encyclopedia on Instrumentation for Industrial Hygiene has been compiled jointly by the Occupational Health Field Headquarters and The Institute of Industrial Health, University of Michigan.

Dust Diseases of the Lung

Although during the last few years reports have appeared on more than a score of rather unusual inorganic dusts that have caused pulmonary injury in workmen, major research emphasis has still been centered on a relative few, chiefly, on silica in its various forms and associated substances, coal, cement, slate, etc.; on asbestos, and, to a lesser degree, on beryllium and vanadium. In the United States in 1952, 528 deaths were recorded (4) from pulmonary tuberculosis associated with occupational diseases of the lung; pneumoconioses, including silicosis, amounted to 1423; similar figures for England reported by Merewether (5) showed 1300 died of pneumoconioses in 1951. Tuberculosis was not the sole disease associated with pneumoconiosis for 16 per cent of 300 workers dead of asbestosis over the years had primary lung cancer also. It is of more than passing interest that the higher rate of cancer in asbestos workers in England is not paralleled in the United States or in Canada, according to Lanza (6). The cause for this difference may lie in the type of asbestos; asbestos is a fibrous form of several different species of minerals, a point often disregarded.

A symposium held in Boston in October 1953 was devoted to occupational diseases of the lung, and laid chief emphasis on silicosis and asbestosis. The pathology of asbestosis (7) was presented, roentgenologic aspects of both diseases (8), clinical observations on asbestos workers (9), its differentiation from other pneumoconioses (10) and the functional abnormalities of industrial pulmonary fibrosis (11).

Current study of the fibrotic diseases of the lung related to occupation may be divided into three areas: (a) contributing factors; (b) mode of development of the silicotic nodule; (c) treatment. Because the literature is so voluminous, both here and abroad, on most of these areas, only the more generally informative reports have been selected.

In a review of factors now believed essential to the production of silicosis, Dautrebande (12) discusses, as important, particle size, amounts of free crystalline silica, the presence of associated dusts and fumes, and breathing patterns. Particles of 3 μ and below in diameter, with special attention to those of 1 μ size, are now generally considered the most injurious from evi-

dence based on human autopsy material and dust-settling characteristics. The electron microscope permits accurate visualization of particles below 1 μ not heretofore possible with light optical systems. Dautrebande, on review of much evidence, considers silicosis a probability if the number of particles is greater than 1.7 mp/cu. ft.;[2] in contrast to this opinion, the current limit believed safe in the United States is 5 mp/cu. ft. (13) as measured optically. Much evidence has now accumulated to indicate that the nature of the substances associated with silica and even extraneous substances may influence greatly the onset and nature of the ensuing silicosis, and especially the particular crystalline structure of the silica itself. King *et al.* (14) have presented evidence on intratracheally injected rats to indicate that, of the various crystalline forms, tridymite was most rapid in producing a tissue reaction, followed by cristobalite, quartz, and fused silica, in that order. The more rapid reaction of the crystalline forms has yet to be explained. In this connection a limited French report (15) on possible pneumoconiosis from silica of fossil origin (amorphous) confirmed the findings of many previous authors who have found no nodular silicosis from untreated diatomaceous earth. A study of the United States diatomite industry by the Public Health Service (16) in co-operation with state health departments of California, Nevada and Oregon, involving five plants and 869 workers, showed, in agreement with past findings, that only one of 25 employees who had worked more than five years exclusively exposed to amorphous silica in the quarry had diatomite pneumoconiosis, but 22 per cent of 286 employed more than five years and working in mills exposed to high temperature calcined, or fluxcalcined, diatomite, showed findings consistent with pneumoconiosis. Calcining diatomite with or without flux (sodium carbonate) converts the far less active variety to cristobalite, a crystalline form, which is believed responsible for the increased response. It was not possible to draw the conclusion that there were any differences in the response to fresh and salt water forms of diatomite.

There is increasing evidence that the onset of silicosis can be hastened by the inhalation of other substances along with silica. The alkalinity associated with sand in a scouring preparation was reported (17) to have caused silicosis in from 20 to 26 months ("galloping" silicosis) in a small group of exposed individuals; the silica dust concentration was tremendously high as far as can be gathered from the original report. Rapidly progressive silicosis has been previously reported in this country (18) from the same cause. Talcosis of unusually rapid development (16 to 24 months) was reported (19) also under circumstances of excessively high talc concentrations. Fluoride, in the form of fluorspar, in mixture with quartz has also been reported (20) experimentally to induce more intense fibrosis than quartz alone, although the latter may be present in only minute amounts (1 per cent) in the mixture.

[2] Million particles per cubic feet of air.

Isolated reports continue to appear with increasing frequency to incriminate many dusts, formerly considered inert, in the production of pneumoconiosis, such as sepiolite (21), corundum (22), feldspar (23), graphite (24), porcelain (25), barita (26), cement (27), mica (28), slate (29), kaolin (30, 31), and a substance to which gas workers are exposed (32).

Several reports in the last few years from the U. S. and England (33, 34, 35) are in agreement that coal miners' pneumoconiosis is an entity distinct from silicosis. Some unknown factor other than inhalation of coal dust, probably an infectious agent, is believed necessary, however, for the development of confluent lesions. The reports indicate a need for reinvestigation of the entire problem of soft coal mining (36). A study of the emotional aspects of respiratory diseases of coal miners has been made by Ross, Miller, Leet and Princi (37); psychoneurosis was the most significant diagnosis in one-third of 40 miners who had been referred to them for special study.

Mechanism.—The solubility theory (38) as an explanation for the formation of the silicotic nodule now appears to be weakening under more critical study. Almost as soon as it was enunciated, much evidence was produced that cast doubt that solubility alone could account for the development of the silicotic reaction. Among the first were experiments contrasting the reactions of the amorphous and crystal forms of silica, which show that highly soluble amorphous varieties were responsible for the toxic reaction, whereas the less soluble quartz produced the fibrogenic reaction (39). It is, of course, commonly known that the tissue reactions produced by amorphous and crystalline forms differ markedly, although the product of solution of each is the same, silicic acid. If silicic acid were solely responsible for the silicotic reaction, then silicosis should develop equally well from amorphous as from crystalline forms. Certainly, if solution of silica occurs, it must be either very limited in amount or localized in area, because no significant differences could be detected, with especially sensitive chemical methods, in the blood or in the urine of silicotics and of normals (40, 41, 42). Values in the urine varied with the acidity; no exact relation between blood and urine values was found, so that silica values could not be considered of either diagnostic or prognostic value. These facts have led to modified solubility theories. Experiments with silicic acid and proteins by Holt & Bowcott (43) showed, indeed, adsorption at the isoelectric points through amino groups chiefly. It had already been shown by German workers (44) that quartz particles become coated with serum constituents with no sign of dissolution, and Scheel *et al.* (45) have shown that the rate of solution of quartz is depressed by protein in such a way as to make it improbable that a simple solution of silica can account for its toxicity as manifested by silicosis. In a further study (46), these authors believed the toxicity may be due to a foreign protein reaction developed from the alteration caused by adsorption on quartz of normal serum proteins as shown by immunologic reactions. This important conclusion would appear to render less significant the opinions of Holt *et al.* (47) that the action of silicic acid in silicosis is a process

of aggregation and disaggregation, depending upon pH, which alters the permeability of tissue membranes. Holzapfel (48) likewise inclines toward the view of the combination of silica with tissue constituents, but has shown specific adsorption with a galactose complex; a galactan, containing only D-galactose, has been isolated from beef lung (49). Similarly, Heffernan (50) rejects the solubility theory, and propounds the surface-valency theory whereby freshly fractured silica surfaces fix large masses of organic material; asbestos acts similarly.

Whatever the final answers to the mechanism may be, the most convincing evidence now favors specific chemical combination of crystalline silica particles with certain tissue constituents, with consequent structural alteration from normal to produce local disturbance and typical silicotic response. Some crucial experiments are needed to confirm these views: (a) actual measurement of crystalline silica particles after many months' residence in the lungs, to determine whether solution occurs, (b) the demonstration that crystalline silica specifically combines with some pulmonary tissue component and can then produce the typical silicotic nodule.

Treatment.—The value of aluminum treatment, and especially the prevention of silicosis, after 10 years of trial, chiefly in Canada, is still open to final appraisal. Unfortunately, good control studies in man are almost nonexistent. Publications on the subject may be obtained from the McIntyre Research Foundation, Toronto, Canada. Dautrebande has proposed a treatment procedure, using a fine aerosol spray of sodium chloride to aggregate the silica particles (51). Animal experiments with this aerosol have shown excellent protective effects; whether field trials now in progress will prove the method of prophylactic value is yet to be reported. In Germany a recent form of treatment of silicosis (52) depends upon the use of electroaerosols consisting of unipolar mists of a calcium-sodium salt solution charged negatively and kept in suspension in an electric field before inhalation by the patients. Claims for effective treatment also have been made for an electroaerosol produced from sea water (53). Intermittent, positive-pressure breathing appears to be the most promising method of affording relief and control of symptoms in the majority of cases of emphysema and fibrosis with dyspnea according to Motley (54). Studies to assess the benefits of the method, however, were reported (55) to be complicated by the use of bronchodilator drugs. When this factor was tested, it was concluded that administration of oxygen and nebulized bronchodilators with improved breathing technics was, in most cases, as good as intermittent positive-pressure breathing.

Organic Dust.—The capacity of organic as well as inorganic dust to produce lung changes has been documented in several reports. *p*-Dichlorobenzene was reported to have produced pulmonary granulomatosis in a middle aged woman (56). Examination of excised lung tissue by polarized light revealed crystals believed to be *p*-DCB. The woman had been using *p*-DCB profusely for from 12 to 15 years on upholstery, carpets, and in clothes-cupboards as an insecticide. Caution has been voiced on the inhalation of resin

dust by Child & Clancy (57); during grinding and powdering of the synthetic resin, dryness of the mouth and nasal mucosa, coughing and sneezing, and other signs of respiratory irritation were in evidence. Experiments in animals produced wheezing, rales, blocking of major bronchi with distended resin granules, and salivation and atelectasis; the most prominent effects were caused from the loosely cross-linked resins. Dust and powder of Teflon (tetrafluoroethylene polymer) have been known for several years to produce a respiratory condition akin to metal-fume fever (58); more recent investigation of the inhalation hazards of heated Teflon (59) showed the evolution of highly toxic fluorine-containing decomposition products. "Printers' asthma" has been reported from England (60) to arise from inhaling a sprayed fluid containing gum acacia. Although considerable study has been given to cotton dust in relation to byssinosis (61), it is not yet clear which of the two structurally related components of cotton dust and associated mold are responsible for the "early" and "late" reactions. In bagassosis the endotoxin of *Aerobacter cloacae* had been proposed as a factor in its etiology (62). Pulmonary disability from the inhalation of grain dust is marked by dyspnea, chronic bronchitis, recurrent bronchial obstruction leading to clinically apparent emphysema, and was reported to occur among those working with seeds and grains for 10 or more years (63). This all-too-brief review of lung diseases from inhaled particulates makes it difficult to escape the conclusion that all dusts, irrespective of their nature, if breathed in sufficient quantity and for sufficient time, may cause profound damage to the lung, and emphasizes the desirability of the physician's obtaining an accurate and thorough occupational history on individuals suspected of pulmonary disease.

Beryllium.—A number of cases of both acute and chronic beryllium poisoning continue to appear, despite the fact that one of the major sources of exposure, beryllium phosphor in fluorescent lights, has been eliminated. In addition, an extremely low air standard of 2 μg.Be/m^3 for continued daily exposure, and no higher than 25 μg. for brief exposures, has long been suggested by the Atomic Energy Commission, one of the greatest users of beryllium. To our knowledge, no cases have appeared to date from the rigid use of these standards which have often been designed into production plants. Because of the peculiarly long latent period for the onset of beryllium disease, only time can tell whether the recommended figure for chronic exposure is a reliable one. The cases that arise are partly from exposures long past, but also partly from beryllium put to new uses such as glass, glazes, and alloys, and a certain number from beryllium production. Partly on the basis of the recent case incidence, Van Ordstrand (64), who was one of those who originally called attention to beryllium disease in the United States, has written of berylliosis as a real but preventable disease.

Diagnosis continues to be a difficult and controversial matter, however. Lieben & Jackson reported (65) that at least one case of their six, formerly diagnosed as berylliosis, was silicosis. Three new cases, two positively identified, one doubtful, have appeared in their factory since their earlier report

in 1948. Some recent cases of beryllium poisoning have been suspected, but none conclusively demonstrated, according to Shilen *et al.* (66) in a study of beryllium extraction, reduction, and alloy fabrication covering a period of 10 years; beryllium concentration in the plant air through the years has ranged from a few micrograms to 600 $\mu g./m^3$. A summary survey of all clinical types of berylliosis observed in a 12-year period has been given by DeNardi *et al.* (67); a total of 431 patients were observed and treated for acute beryllium intoxication. Curtis (68) states that dermatitis due to beryllium is of an allergic-eczematous type, with the beryllium ion believed to be the sensitizing allergen. The patch test has been used with success in a limited number of cases as a diagnostic test of beryllium granuloma of the lung; a positive test was always found with true beryllium involvement, while negative results were obtained in Boeck's sarcoid and in normal beryllium workers. A registry to collect and correlate data on cases with beryllium poisoning is being accumulated by Dr. Harriet Hardy at the Massachusetts General Hospital, Boston. Work is continuing by Schubert and co-workers (69) on the mechanism of protection of aurin tricarboxylic acid in beryllium poisoning; ACTH treatment has provided no lasting beneficial effects, but Hardy (70) believes that either adrenocorticotrophin or cortisone is of real value in controlling symptoms though not in curing the disease.

Vanadium.—The study of vanadium compounds in relation to respiratory disease has been given serious attention since 1952 for two reasons: first, the mining and milling of unprecedented quantities of carnotite ore ($K_2O \cdot U_2O_3 \cdot V_2O_5 \cdot H_2O$) in this country in connection with securing uranium for atomic energy purposes has increased the number of exposed individuals; and second, the finding of respiratory illness among workers producing vanadium compounds for high-grade steel and other purposes, by Sjoberg (71) and by Roschin (72), as well as among workers cleaning boilers fired with vanadium-bearing oils, by Williams (73), Sjoberg (74), and by Fallentine & Frost (75), and from gas turbines [Browne (76)]. Sjoberg has written a monograph (77) in English on the health hazards in the production of vanadium pentoxide. The responses to air-borne vanadium dust are: slight irritation of the conjunctivae; slight or copious rhinitis, with acute or chronic hyperplastic changes in the nasal mucosa; dryness or irritation of the throat, with chronic atrophic, and sometimes also acute, changes; hoarseness; only mild acute changes in the mucous membrane of the larynx, and a cough as the most outstanding symptom, often with many rhonchi, although bronchoscopic examination shows only mild bronchitis. Pneumonia has been diagnosed in several cases and was considered to be of chemical-bacterial origin ("vanadium pneumonitis"). The responses are thus acute, not chronic, temporarily incapaciting, but not fatal. Dermatitis is not a common feature of vanadium exposure.

Experimental research on the systemic effects of vanadium compounds carried out in laboratories of the Occupational Health Program, United States Public Health Service, has shown that vanadium is capable of inducing at extremely low tissue concentrations (1 $\mu g/g$ of tissue) derange-

ments of basic metabolic processes which are not manifest clinically or felt by the worker. It has led to a highly sensitive test of pretoxicosis and to conclusions of practical value in the management of the health of vanadium workers. The critical feature of the pretoxicosis test is that the cystine content of the nails is depressed following chronic low-grade exposures to vanadium (78). Amounts of urinary vanadium resulting from exposure may amount to no more than 20 to 30 μg per l. when cystine depression occurs, according to a sensitive analytic method developed in these laboratories and reported by Talvitie & Wagner (79). Another important observation was that diet plays a deciding role in the toxic response. Complete, well-fortified diets have been shown experimentally to counteract the potentially toxic effects of vanadium, whereas borderline diets failed to do so, suggesting the value of nutritious and well-balanced diets for vanadium workers. The basic cause of the dietary differences has not yet been determined; metal antagonism, vitamins, or other factors may be responsible. Certainly vitamins exert a beneficial effect, for it has been shown (80) that ascorbic acid can counteract the effect of lethal doses of vanadium compounds in animals, if administered in small repeated doses within a short period after the fatal vanadium dose. Vanadium has also been shown capable, at nontoxic vanadium levels, of reducing elevated plasma cholesterol in rabbits fed high cholesterol diets (81). Reduction in arterial plaque formation was associated with this response. The significance of the role of vanadium in atherosclerosis requires further elaboration. Possibly the most interesting aspect of this entire research is that vanadium is merely one of a number of similar substances to which man is continually being exposed, through contaminated air, water and food, from which trivial amounts of materials may cause deep-seated metabolic alterations in the body.

Edathamil in Metal Poisoning

Poisonings from a variety of metals are still being reported, although the proportion of cases occurring in the United States in relation to worker exposure is decreasing; this does not appear to be the case in foreign countries. Of the metals, lead is now receiving renewed interest. The surge of interest arises for three reasons: (a) several cases of lead poisoning, some fatal, among children eating painted lead surfaces have been recognized in many of our larger United States cities; (*b*) a new and effective method of treatment has been found in a chelating agent, ethylene diamine tetraacetate, (EDTA) which has been given the generic name of Edathamil, by the Council on Pharmacy of the American Medical Association; (*c*) case of lead intoxication are still being seen in some smelting operations, brass foundries, auto-body shops, lead storage-battery plants, and printing establishments.

Reported cases of infant mortality from lead are as high as 30 per cent, increasing to 65 per cent when complicated by encephalopathy (82). Stimulated by facts like these, the American Standards Association has drawn up specifications to minimize hazards to children from residual surface-

coating materials; this activity was sponsored by the American Academy of Pediatrics. It is small wonder, therefore, that early reports of the effectiveness of EDTA in children (83, 84, 85) were recieved enthusiastically. The more recent excellent report of its use in adults by Sidbury (86) would seem to leave little doubt of the value of EDTA in lead poisoning. This report presents a review of the action of EDTA with reference to papers showing its distribution and excretion in man and in animals, dosage-schedules, and case reports with lead-excretion curves following therapy. The value of a chelating agent such as EDTA is its capacity to combine with metals so as to render them un-ionized. The combination often has reduced toxicity and allows an increased rate of excretion via the kidneys. EDTA is used as the calcium salt because this form eliminates the development of low-serum-calcium tetany. As with most drugs, there may be obvious dangers from prolonged, wanton or excessive use. Dudley *et al.* (87) have already described toxicologic changes associated with the use of EDTA in treating hypercalcemia: "At autopsy, unexpectedly severe damage occurred to the renal tubules with engorgement of the reticuloendothelial cells with gross eosinophilic granules and hemorrhagic manifestations." Kehoe (88) has considered as unwarranted the continued use of EDTA as a prophylactic measure for lead workers as a substitute for reduced lead air levels in the workroom. Preparations for such use would be orally administered where absorption has been shown to be minimal (89); hypotheses, and not proof, have been offered to explain EDTA's action by the oral route.

Edathamil has been experimentally tested in mice for its effectiveness in manganese poisoning (90); it prevented the disease from progressing, but did not reverse the serious effects of manganese on the nervous system. Edathamil has been reported (91) to accelerate the excretion of plutonium in man, especially directly after plutonium intake and "offers promise in a situation formerly considered hopeless." CaEDTA was reported (92) to decrease the excretion of mercury in a single case of combined mercury and lead exposure in which the patient was successively treated with dimercaprol and EDTA. Fatal doses of vanadium administered to experimental animals were successfully counteracted by later treatment with CaEDTA (93). Edathamil has also been shown experimentally to increase excretion of yttrium and americium (94) and zinc (95). CaEDTA, combined in an ointment, has been reported by Maloof (96) to be of value in the treatment of chrome ulcers; EDTA loosens and permits easier removal of the ulcer base in at most two or three applications. EDTA has also been recommended in the treatment of lime burns of the eye (97).

Solvents

The last few years have witnessed a gratifying trend generally in the approach to the development, marketing, and use of the safer solvent. The contact of industrial workers with solvents is probably the greatest of any single group of substances; their injurious effects range from extreme hazards

of explosion and fire and serious and fatal injuries, to dermatitis. The awareness of the hazards of solvent use has greatly increased in recent years because of the increase in toxicologic information and education on the risks involved. This knowledge has served to curtail the use of many of the more hazardous solvents: the highly flammable solvent is now less commonly used without admixture with a nonflammable component; the seriously toxic benzene is restricted to limited and controlled uses, and the less hazardous toluene or xylene substituted for it; several safer chlorinated hydrocarbon solvents are now substituted for carbon tetrachloride. The hazards of carbon tetrachloride are considered so great that some companies have forbidden its use, or, if permitted, require experienced supervision, or usage limited to small quantities. Unauthorized or flagrant use still persists, however, as two recent excellent reviews testify (98, 99). Supportive treatment of severe CCl_4 intoxication now emphasizes, in addition to attention to the liver injury, the management of renal tubular damage with its possibilities of pulmonary edema and potassium intoxication. Death frequently results from the last. It is now clear also that many of the severe and fatal cases of poisoning involve chronic alcoholics or individuals who have ingested alcohol prior to, during, or after CCl_4 exposure. Despite the known potentiation of toxicity of halogenated hydrocarbons by alcohol, the chief approach to safer solvents is the use of chlorinated hydrocarbons of lesser toxicity than CCl_4, namely, trichloroethylene (TCE) (100), perchloroethylene (101) and, more recently, methyl chloroform (102); the threshold limit values for these agents are, respectively, 200, 200 and 500 p.p.m. in comparison with 25 p.p.m. for CCl_4. These threshold limits provide a rough indication that some hazard remains even with the use of these substitutes; indeed, cases of fatal exposure to TCE have been reported (103), but exposures were far in excess of the threshold limit, presumably several thousand p.p.m. Study is being given the excretion products of TCE, especially trichloroacetic acid (TCA) (104) as a measure of exposure, but the results and interpretations are complicated by the variability of the liver's capacity to metabolize the TCE. Some authors conclude that TCA cannot be used as a simple test of exposure to TCE (105). Another solvent, methylal (dimethoxymethane), of relatively low toxicity with a threshold limit approximating 1000 p.p.m. (106), appears to have received less attention and use, possibly because of its high volatility and flammability.

Other approaches have been made toward so-called "safety" solvents. One such approach is the use of the azeotropic mixture (107) whereby a constant b.p. for all components is achieved. This has the practical advantage that the vapor from the mixture has the same composition as the original mixture, thus permitting a more exact knowledge of the composition of the exposure vapors and preventing the disproportionate build-up of vapor concentrations of the more volatile substances. The use of solvent mixtures as a substitute for the single solvent is now common with all producers, the components of the mixture being selected for their nonflammability and lowered

toxicity. A typical solvent mixture now on the market is methylene chloride 25 per cent, perchloroethylene 5 per cent, and Stoddard Solvent 70 per cent, having a threshold limit approximating 500 p.p.m. Associated with the use of solvent mixtures is the question of the synergistic effect of the combination wherein the total toxicity may be greater than the sum of that of each component. Such effect is believed to occur from mixed exposures to methyl alcohol and methylene chloride, or carbon monoxide and many of the halogenated hydrocarbons, and there are others. LaBelle (108) has shown that particulate substances may enhance, decrease, or have no effect on the toxicity of a vapor, depending on its nature. The same worker (109) showed also that the toxicity of a solvent mixture of eight components was essentially that of its chief (55 per cent) component, methyl ethyl ketone. Likewise, McCollister (110), working with various fumigant mixtures of ethylene dichloride and dibromide and CCl_4, showed that the toxicity of the mixture could be mathematically predicted from the composition, i.e. no synergistic effect. Thus, whereas one should always be mindful of the possibility of synergistic effects of mixtures, synergism is by no means a necessary consequence of mixtures.

A new group of "OXO" solvents is now being marketed, so-called from the process that adds oxygen to unsaturated olefins to make a series of unsaturated aldehydes and alcohols that will have large application as paint and varnish solvents, components in safety glass, vitamin intermediates, and many other uses. Price margins in this field being small, and purification being costly, mixtures of these "OXO" solvents may be customary in the coming years.

A number of solvents are used as vaporizing liquids for fire extinguishers. CCl_4 is by far the most common and important; however, other halogenated hydrocarbons are being introduced as replacement for, or in combination with, CCl_4 (111). Of the newer agents chlorobromomethane has received the widest usage; the hazards of this liquid are somewhat less than that of CCl_4 (112), the main advantage in firefighting being that CH_2ClBr can be used at lower temperatures and is not as corrosive on metal extinguishers.

Air Pollution

The increasing importance of this subject to occupational health would appear to justify greater space than has been heretofore allotted it (113). Now, after six years of research and study and an overabundance of discussions and symposia, three major areas of accomplishment appear to have emerged. Much is now known of the nature and amounts of solid particulates contributing to the air pollution of many cities, both in the United States (114–118) and abroad (119). The total particulate load in the air over many United States cities ranged from 200 $\mu g/m^3$ in residential areas to 500 $\mu g/m^3$ in the air over industrial areas, of which identifiable metallic constituents accounted for from 5 to 10 per cent; the bulk of the remainder was carbonaceous material. Considerable uniformity of the particulate matter in the

air from city to city was found, and the more toxic elements, such as Pb, Mn, Cr, As, Be, etc. were invariably less than 1 $\mu g/m^3$ on the average, and although unquestionably contributing to over-all body burden, these levels were well below those usually considered hazardous. Recently, however, new importance has been attached to the water-soluble fraction of these particulates by Hemeon (120), to which he ascribes the capacity of respiratory irritation. In this connection, it should be noted that the particulates over cities with little or no industry were similar in nature and only somewhat smaller in amount than over areas with high industrialization (121). This is expected, as many elements (Ti, Mg, Si, Al, Fe, Ca, Pb, etc.) are common to soil, rock, cement, and paint that find their way into the air by attrition.

In the continuing search for evidence, that still proves elusive, of the long term effects of air pollutants on human health, a second possibly important area was developed in the demonstration, first in England (122, 123), and later in the United States (124), of atmospheric carcinogens; a large number of the commonly recognized polycyclic aromatic carcinogens have been identified in the atmosphere and in gasoline engine exhausts. Whether the amounts found in the general atmosphere (less than 1 $\mu g/m^3$) are sufficient to induce lung cancer in man is still to be demonstrated. They have been shown, however, capable of causing skin cancer in mice (124). Other types of air-borne carcinogens such as printing inks (125) have also been implicated as causing bronchial carcinoma (Stockholm); and rubber tire dust, also carcinogen-containing, has been found in appreciable quantities in the air of our largest city. Rather detailed inventories of automobile gases have been made (126), and the distribution of these gases in city air estimated (127). It is estimated that of the more than 2000 tons of total hydrocarbons evaporated into the air of Los Angeles each day, 440 tons are unsaturated hydrocarbons, of which 220 tons arise from autos and service stations, and the remainder from gasoline production; smoke particulates from auto exhausts are estimated at 50 tons per day.

The third major contribution to the understanding of air pollution is the demonstration of certain basic reactions of aerosols, by Haagen-Smit and co-workers (128), for Los Angeles air, namely that oxidants are the chief contributors to eye irritation and crop damage. Potential oxidants arise in the air from natural and man-made sources through a complex set of chemically and photochemically catalyzed reactions involving oxygen, nitrogen oxides, and hydrocarbons. Among the products detected, and they are numerous, ozone and oxygenated hydrocarbons (peroxides) are considered to be the serious offenders. More recently Haagen-Smit has demonstrated that ozone may be photochemically generated from auto exhaust gases (129). It has long been known (130) that combustion engines are capable of forming nitrogen oxides by fixing the nitrogen in the air and, like unburned hydrocarbons and ozone, the quantities formed depend upon operating variables (131). This, and related information (132), has provided speculation on the possibility of either better engine design for more complete burning of fuel,

or the use of selected types of fuel that will not yield oxidizable, potentially eye-irritating hydrocarbon derivatives in the exhaust.

It is hoped that a greater proportion of future research on air pollution will consist of the study of the basic reactions of aerosols (synthetic approach), for it is wholly possible that the conventional methods of sampling and analysis of the atmosphere will completely fail to detect or identify the more highly reactive and transitory types of pollutants that will prove ultimately to be the worst offenders. It is probable also that still more potent, elusive, and unusual types of air pollutants are yet to be discovered (133). By a combination of both approaches, however, greater assurance of obtaining the objectives will be had.

The question of the chronic effects on health is still awaiting development of tissue function tests specific enough to differentiate between the effects of air pollutants and those of tobacco smoke, infectious processes, aging, etc. Epidemiologic surveys are suitable for indicating the areas for investigation, but final proof that air pollutants cause injury to organ systems must rest on direct objective evidence from tests of functioning of the affected organ.

Ozone and Oxides of Nitrogen

Because ozone has an essentially "clean" odor, ozonizers are periodically recommended for their air-cleansing value in hospitals, homes, offices, and garages. Ozone also is found associated with many industrial activities, such as welding, electrostatic precipitators, or other electric-generating devices. Because of ozone's powerful oxidizing action it is now being used in the fine organic chemical industry, in water purification, and in cheese storage rooms. These uses have led to an increased number of potentially serious exposures to a substance long known for its toxicity. Moreover, the role of ozone in Los Angeles smog has lately assumed major proportions. Recently, however, a new note in the toxicity picture of ozone was injected by Thorp (134), who claimed that the oxides of nitrogen associated with ozone production were responsible for the observed toxicity. Refuting evidence was recorded by Weaver (135) in a brief review on ozone toxicity. Because of the danger that Thorp's statement could be misinterpreted and misapplied (and, indeed, such statements have found their way into recent toxicology texts (136), the present author undertook a review and study of the problem of the relation of oxides of nitrogen to ozone toxicity. The review (137) showed no convincing evidence to support the contention that the oxides of nitrogen would account for ozone toxicity, chiefly because, under usual circumstances of ozone generation, only small amounts (usually 1 or 2 per cent or less) of nitrogen oxides are produced. Animal studies (138) further showed that addition of oxides of nitrogen to ozone up to 50 per cent failed to alter the toxicity of ozone, the LD_{50} of which for mice approximated 4 p.p.m. for 6 hr. exposures. In support of these findings, Gray, in a series of studies (139) on the oxides of nitrogen (chiefly NO_3) produced from red fuming

nitric acid, found the LD_{50} for rats to be approximately 75 p.p.m., and suggested the safe level for daily exposure for man to be 5 p.p.m.; this latter value has been incorporated into the threshold limits of the American Conference of Governmental Industrial Hygienists. The matter, however, appears still unsettled, for reports from England by Diggle & Gage (140) claim a toxicity for nitrogen pentoxide somewhat greater than that of ozone; the importance of N_2O_5 is that it is the product resulting from NO_2 in the presence of excess ozone. The experiments of Diggle & Gage were complicated by a variety of factors, and seem to this reviewer not to support the conclusions of the authors; certainly, more work must be done to attempt to reresolve this controversial and difficult problem. Part of the difficulty has undoubtedly lain in the inadequate sampling and analysis procedures. To overcome these difficulties Byers *et al.* have critically evaluated and modified the method of Smith and Diamond (142) for ozone, and Saltzman (141) has developed a highly sensitive and accurate method of sampling and analyzing nitrogen dioxide. Other difficulties may also stem, as suggested elsewhere in this review, from varying conditions of humidity, or the presence of as yet undemonstrated free radicals of a highly toxic nature, and these may prove responsible for the differences in the present experimental conclusions.

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SYMPATHETIC BLOCKING AGENTS[1]

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Until approximately a decade ago a sympathetic blocking agent was little more than a scientific curiosity but today the picture has been considerably altered; certain sympathetic blocking chemicals have come into their own as valuable therapeutic agents. They have become available to us through the fine cooperation of our research scientists, a group which includes the chemist, the biologist, and the clinical investigator. In the development of these important drugs as available to physicians today is the pharmacologist who early recognized, with the inquisitive clinician, the important role that sympathetic predominance plays in the symptomatology of certain disorders which reflect imbalance of the autonomic nervous system. Some of these include neurogenic hypertension, certain peripheral vascular diseases, especially Raynaud's and probably Buerger's disease, herpes zoster, hyperthyroidism, tachycardia, glaucoma, exophthalmia, migraine headaches (spastic type), neurodermatoses, renal hypertension (in part neurogenic in origin?), vasospastic dysmenorrhea, causalgia, and probably some types of epilepsy.

There is little doubt today that the autonomic nervous system plays a very important role, either directly or indirectly in many diseases, in terms of overactivity or underactivity of either portion of the autonomic nervous system, that is, of the parasympathetic or the sympathetic divisions. Our attention at the moment is directed toward suppressing, within desirable physiologic limits, the overactivity of the sympathetic portion of this system in certain undesirable conditions. This goal can be achieved by certain recently developed chemical compounds which have already established their value as therapeutic agents.

Inspection of Fig. 1, a diagram by Hafkenschiel & Sellers (1), which is an excellent modification of that previously employed (2), reveals various focal points of attack in the establishing of sympathetic or adrenergic blockade. The synonymous or interchanging use of the terms sympathetic and adrenergic blockade, a procedure which will be followed throughout this presentation should be noted. Adrenergic refers to that portion of the autonomic nervous system, namely the sympathetic portion, which responds to the action of adrenaline or adrenaline-like substances. These include epinephrine and norepinephrine in particular; any agent that blocks these substances which act in the region of the final arborization or distribution of sympathetic nerve fibers, that is, within the receptive substance of the end organs associated with sympathetic innervation, is classified as a sympathetic or adrenergic blocking agent. On the other hand, one must bear in mind that

[1] The survey of literature pertaining to this review was completed in June, 1955.

every sympathetic nerve pathway, once it leaves the spinal cord by the spinal ventral nerve root, must traverse either a primary or secondary sympathetic ganglion; the only known important exception to this general rule is that unique sympathetic pathway which passes out to the adrenal medullary substance, in which case the latter can be considered as the postganglionic component of the pre- post- ganglionic synapse within a sympathetic nerve pathway. Obviously, the chemical substance which mediates and facilitates the transfer of impulses across normal pre- post-ganglionic synapses is acetylcholine; it can be blocked in therapeutic dosages, not by atropine as anticipated, but by ganglionic blocking agents to be referred to subsequently. Then too, any drug or compound which may arrest

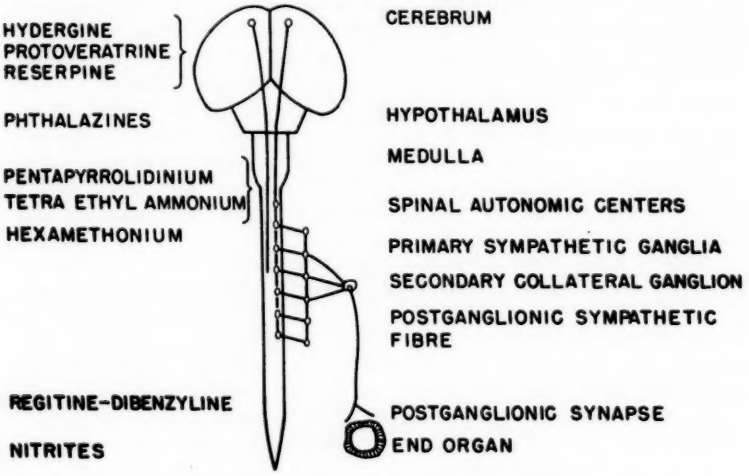

FIG. 1. Possible sites of action of depressor drugs.

or dampen the outflow of sympathetic impulses from their central points of origin within the brain stem, that is, within the hypothalamus or medulla oblongata, may still be classified rightfully as a sympathetic or adrenergic blocking agent in that it tends to defeat the undesirable condition known as sympathetic predominance.

It is conceivable that certain chemical compounds now available as therapeutic agents may act in more than one area in terms of their adrenergic or sympathetic blocking effects, but we should like to present these important drugs in the order of their chief locus of activity, stressing to be sure not only their areas of associated pharmacologic action, but also emphasizing the advantages or disadvantages of such varied types of activity. The discussion will begin with the central autonomic depressants, that is suppressants of the central nervous system, with special emphasis on sym-

pathetically controlled vasomotorial mechanisms associated with the control of blood pressure and heart rate in particular, but with some emphasis also on other types of central control. Next discussed will be those agents which act as ganglionic blockers and last will be those known as peripheral blockers of sympathetic controls of blood vessels and other end organs.

Central Autonomic Depressants

Rauwolfia and reserpine.—One of the most striking advances in modern therapy is that associated with the development of the old Indian drug known as *Rauwolfia serpentina.* This development parallels and in a sense supersedes the rapid development of chemotherapy in reference to sulfonamides and antibiotics. It would seem that in terms of over-all benefit to the greatest number of patients the scientific studies of Rauwolfia and applications in various forms (including those of some of its chemically different but pharmacologically similar relatives such as chlorpromazine) would justify the statement that the humble Rauwolfia plants have opened up one of the most promising decades in modern medicine.

Vakil (3) gave us one of the first accurate and scientific appraisals of Rauwolfia [Bhatia (4); Gupta *et al.* (5); Roy (6)]. This was soon followed by the work of Wilkins and his associates (7) and, within the last two years, several hundred important papers have already appeared reporting on the experimental and clinical features of Rauwolfia or of its important alkaloids such as reserpine [Müller *et al.* (8); Bein *et al.* (9); Plummer *et al.* (10)], deserpidine [Schneider *et al.* (11)], and rescinnamine [Cronheim *et al.* (12)]. From the work of Wilkins (7) and others it would seem that reserpine represents the major action of the whole crude drug in *Rauwolfia serpentina* form; he states that reserpine, unit for unit in terms of therapeutic activity, is about 1,000 times more potent than its mother substance, *Rauwolfia serpentina.* Somewhat similar statements have been made recently by Tuchman & Crumpton (13) who appraised potency relationships as 1:500 and 1:750 rather than at 1:1,000.

The mechanism of action of reserpine or Rauwolfia is indeed intriguing. The alkaloid reserpine was studied early by Bein and Plummer and their respective associates (9, 10), as well as by Schneider & Earl (14). These studies reveal that the following effects of reserpine are significant:

(*a*) Quietude and reduction of emotional response.

(*b*) Relaxation of the nictitating membrane.

(*c*) Bradycardia with hypotension.

(*d*) Miosis.

(*e*) Hypothermia.

(*f*) Augmented intestinal activity (and emesis in pigeons).

(*g*) Increased secretion of gastric juice and hydrochloric acid (after intravenous injection).

(*h*) Little or no effect on the electroencephalographic pattern (unlike barbiturates).

From a pharmacologic point of view reserpine has little if any peripheral anti-adrenergic or sympathetic blocking activity. Peculiarly, and fortunately, it seems to have a strong capacity to block central sympathetic emission of impulses from the region of the hypothalamus and upper medulla; in other words, it is a central blocking agent of sympathetic outflow, but its central depressant effect is elicited in a manner apparently different from that produced by barbiturates and other cerebral sedatives.

By suppressing sympathetic outflow at its source within the central nervous system, peripheral resistance is thereby reduced in a generalized manner, thus accounting for varying degrees of vasodilation with its associated hypotension. Simultaneously, parasympathetic influence is permitted to predominate; one feature of this is augmented vasodilation on a cholinergic basis, thus adding to the hypotensive value gained from the primary release of central sympathetic vasoconstrictor control of the blood vessels. Direct vascular relaxation [Tripod *et al.* (110)] may also contribute to reserpine-induced hypotension.

Another evidence of central sympathetic inhibition, with its attending parasympathetic predominance, is that of bradycardia. This effect is one of the most desirable associated with the use of reserpine or Rauwolfia and has been well utilized by Wilkins (7) and others in the treatment of tachycardia which attends the use of hydrazinophthalazine in hypertensive patients. Recently this bradycrotic effect has been favorably exercised in mitral stenosis [Schumann (15)], atrial fibrillation (16), and hyperthyroidism [Renzi (17)]. Because the bradycrotic effect of reserpine or Rauwolfia is exercised through the vagal control of the heart, other vagal influences could be anticipated and these are actually experienced as manifest in the hypermotility of the gastrointestinal tract, sometimes (but rarely) to the point of frank diarrhea. This gastrointestinal effect, however, has been favorably employed and commented upon by Harris (18), especially in geriatric patients.

Gastric hypersecretion can be demonstrated in experimental dogs with gastrostomy following intravenous administration of reserpine [Plummer *et al.* (10)]. This is completely nullified, however, on a dose response basis by means of atropine or atropine substitutes such as methantheline (Banthine), oxyphenonium (Antrenyl), and so forth. Bachrach (19) has reported similar reactions to reserpine in some of his clinical subjects following intravenous administration of high dosage; and he states: "Injection of 1 mg. of Serpasil uniformly stimulates gastric secretion of acid and pepsin in the human, whereas oral administration of therapeutic doses (0.5 to 4 mg. daily) of this drug over many months apparently does not bring about a similar action." On this basis it would seem that the favorable peripheral action of such anticholinergic substances as atropine and its synthetic substitutes given orally might be reinforced by the central tranquilizing action or oral reserpine on the premise that emotional influences, if they have any part whatsoever to play in terms of psychosomatic relationships, could be dampened at their source. Furthermore, in the event that oral reserpine might

produce in some patients (contrary to Bachrach's findings) gastric hypersecretion in terms of volume and acid, hypermotility, or both, these might be successfully antagonized peripherally by the atropine-like action of the anticholinergic agent employed simultaneously. Such studies are now in progress.

In a later section dealing with hydrazinophthalazine the point is made that Wilkins (20) had successfully employed the central dampening effects of reserpine on sympathetic outflow on two counts, namely, the decrease of peripheral resistance permitting augmentation of the peripheral effects of hydrazinophthalazine, and the bradycrotic effects which tended to nullify the Apresoline-induced tachycardia while simultaneously permitting reduction of the dose of the latter drug. Thus Wilkins was able not only to augment the action of hydrazinophthalazine by reserpine but also he could reduce the dose of the former drug, thus minimizing the potential onset of any disturbing side reactions associated with the administration of hydrazinophthalazine per se.

More recently Smirk *et al.* (21) have reported on the successful use of reserpine and pentapyrrolidinium (Ansolysen). Smirk thus employs sympathetic blockade at two levels, namely, centrally, and at the sympathetic ganglionic level peripherally, an ingenious approach. In this practice Smirk obviously adds markedly to reserpine's hypotensive virtue by the strong sympathetic blocking action of pentapyrrolidinium and he rightfully cautions about the dangers associated with such dual approach to the problem. On the other hand, his results are such that one cautiously employing his method of central and peripheral blockade may experience similar satisfaction in the treatment of severely afflicted hypertensive patients. Similar reports have appeared in respect to the use of Rauwolfia derivatives and hexamethonium (22, 23). From preliminary reports Serpasil and chlorisondamine (Ecolid) [Winsor (24)] would seem to be likewise similarly promising.

For the treatment of the hypertensive patient there are many other mixed preparations now available in the form of either Raudixin, Rauwiloid, or reserpine, combined with other hypotensive agents such as Veriloid, phenobarbital, aminophylline, organic nitrates such as mannitol hexanitrate, ganglionic blocking agents, hydrazinophthalazine, etc., each with its own advantages or disadvantages. It would seem that with the abundance of various types and combinations of antihypertensive agents available, we are finally in a position not only to give our patients symptomatic relief but probably also to prolong their lives [Smirk (25)]. In this regard the writer would like to commend to one's reading the excellent contribution of Schroeder entitled, "Why Not Control Hypertension with Drugs?" which appeared recently in *Clinical Research Proceedings* (26).

As important as the use of reserpine or Rauwolfia in certain forms is today in the treatment of the hypertensive patient, the greatest application of this group of drugs undoubtedly will be in the treatment of manifestations of anxiety states other than neurogenic hypertension [Yonkman (27, 28);

Schroeder & Morrow (49)]. Whether the benefits achieved can be due entirely to sympathetic blockade is difficult to state at this time but the unique properties of reserpine and the new synthetic agent, chlorpromazine (Thorazine), to shield the hypothalamus and upper medulla not only from peripheral reflex excitation but also from cerebral bombardment, set these drugs apart in terms of their extraordinary pharmacologic activities. Truly, they may insulate in part not only a segment of the central nervous system against afferent stimulation but the individual in toto against his environment. Much is still to be heard about these drugs and many of their related counterparts now in research development.

The side reactions associated with reserpine and Rauwolfia therapy are not numerous but are of some significance. These include lethargy, nasal stuffiness, gastric hypersecretion, hypermotility of the gastrointestinal tract, nightmares, and in some cases a melancholic type of depression; most diminish or disappear on reduction of dosage. Nasal stuffiness can be nullified in part by the concomitant use of antihistamines [Freis *et al.* (29)] or topical application of various vasoconstrictors [Dustan *et al.* (30)], but as a rule this undesirable nuisance which is disconcerting and uncomfortable disappears within a matter of a few weeks to a month or so. Hypersecretion and gastric hyperirritability can usually be diminished or nullified by reduction of oral dosage or perhaps by concomitant anticholinergic therapy, as demonstrated in animals (10). The more serious situation, that of melancholic type of depression [Freis (111); Orgain (112)], usually can be corrected readily within a few days by withdrawal of the drug or reduction of the dosage [De Kruif (113)].[2] Furthermore, it can be favorably antagonized in some instances by concomitant use of ephedrine, amphetamine, or phenidylate (Ritalin) [Ferguson (31)]. In any event there seems to be little doubt that the advantages achieved with Rauwolfia therapy far outweigh the disadvantages associated with the appearance of an occasional case of depression, especially in view of the fact that such depression can as a rule be readily counteracted.

Another very disturbing and important undesirable reaction to Rauwolfia is that of a Parkinsonian syndrome of varied intensity [Kline *et al.* (32)]. The same, peculiarly enough, also has been reported after chlorpromazine [Bleuler *et al.* (33)]. This side reaction diminishes or disappears on reduction of dosage or upon withdrawal of the drug.

In conclusion, reserpine represents a most valuable and yet very strange drug. It is an alkaloid but completely devoid of taste in contrast to all other alkaloids which are bitter, some to a most disagreeable degree. Reserpine is

[2] "From my experience so far I would say that it is extremely important to obtain some evaluation of a patient's emotional status before starting Serpasil. I do not think that Serpasil is the primary cause of these depressions but rather that it initiates a depressive reaction in some people who are susceptible to such; for example, people who have a good pattern for involutional melancholia. These experiences have not in the least lessened my enthusiasm for Rauwolfia and I am using it as a basic drug for almost all my hypertensives, as well as in some anxiety states."

therapeutically one of the most active alkaloids known, microgram for microgram, and yet the safest of all. Hubbard (34) reports a case of a twenty-month old youngster who ingested 260 mg. of the pure substance without apparent ill effects; the chief feature was some intensity of sedation during his nap periods. When one considers that the average adult dose for the patient who has a mild case of the so-called jitters or is mildly tense is only 0.1 to 0.2 mg. per day, one appreciates the safety factor associated with reserpine therapy in the light of the youngster's experiences as described by Hubbard. The youngster's ingestion of a total of 260 mg. of reserpine is 2,600 times the daily 0.1 mg. dose employed by many patients for mild sedation. Furthermore, this child was approximately 25 pounds in weight. In terms of a 200 pound patient on a dose of 0.1 mg. per day the child received on a weight basis approximately 20,000 times the adult dosage. Not only for all practical purposes is reserpine very safe, but it is also nonaddicting despite its capacity for the production of a reasonable sense of well being. As a centrally acting sympathetic blocking agent it would seem to lend itself to successful application in many harmful psychosomatic relationships.

Hydrazinophthalazine (*Apresoline*).—The pharmacologic action [Gross *et al.* (35); Craver *et al.* (36); Walker *et al.* (37)] of this substance and its relatives is most varied and complex. It was early thought that it could exert a direct action on blood vessels similar to that of nitrites and it was soon learned that it had very mild anti-adrenergic action. It is now considered, however, that the latter action is so little as to be only very slightly accountable for any associated drop in blood pressure. In effecting a drop in pressure it is conceivable that this drug may immobilize either angiotonin or pherantasin [Schroeder (38)]. A very significant action of hydrazinophthalazine is that of unique renal vasodilation [Reubi (39)], a feature which was early applied to the treatment of hypertension associated with toxemia of pregnancy by Assali (40) and others.

Hydrazinophthalazine inhibits the action of diamine oxidase [Gross *et al.* (41)], thereby permitting abnormal amounts of endogenous histamine to become available for physiologic use. Theoretically, this histamine could contribute to the relaxation of peripheral vessels but any part played in this direction is probably quite minimal as antihistaminic agents do not interfere significantly with the peripheral vasodilating effect of hydrazinophthalazine. On the other hand, the hydrazinophthalazine-induced types of headaches as described by Schroeder and others are relieved in part by antihistamines (42) or by institution of therapy with very small doses of the offending vasodilating agent [Rogers *et al.* (107)].

Hecht's group (43) is of the opinion that hydrazinophthalazine exerts its hypotensive action primarily because of its strong vasodilating effect, especially in the splanchnic area. They compare the action of hydrazinophthalazine with that of the vasodilator components of epinephrine.

Still another mechanism of action is that proposed by Taylor, Page & Corcoran (44) which refers to the antagonistic action of hydrazinophthala-

zine to that of a vasoconstrictor substance which they describe as cerebrotonin. Their hypothesis rests on the premise that the central nervous system, particularly the brain, under certain conditions produces a substance which acts in a manner similar to that of the well-known vasoconstrictor, serotonin. Their conclusions, which are based on clean-cut experiments in anesthetized dogs, have not generally been accepted as yet but they present a most interesting, and it would seem a quite plausible, explanation for at least some of the pharmacologic and therapeutic action of hydrazinophthalazine.

There is other evidence of some probable central action of hydrazinophthalazine and this was first presented by Freis and his associates (45) as gained from their clinical studies which indicate that the bradycrotic effects of norepinephrine, following intravenous administration, are appreciably diminished after the administration of hydrazinophthalazine.

Despite the above evidence of the central action of the hydrazinophthalazine molecule, many investigators prefer to classify hydrazinophthalazine as a peripherally acting agent; furthermore, although this drug exhibits mild anti-epinephrine or anti-adrenergic actions, it would seem that its chief peripheral vasodilating effect is that of a direct action on the blood vessel wall.

Another dramatic action of hydrazinophthalazine is that of antagonizing the vasculotoxic action of renin in steroid-sensitized animals. This action is manifested by the fact that administration of the drug provides almost complete protection from the otherwise lethal consequences of the "eclampsia-like syndrome" of Masson, Corcoran and Page [Renzi & Gaunt (114, 115)]. In addition, hydrazinophthalazine suppresses or modulates adrenocorticoid-induced hypertension in rats as demonstrated by Gaunt *et al.* (116, 117). This agent delays the onset of that usually lethal type of hypertension that results from chronic administration of DCA[3] or cortisone as abetted by sodium chloride in drinking water. If, however, hydrazinophthalazine is supported by reserpine, Gaunt and his associates observed not only remarkable protection against corticoid-induced hypertension but a failure of its development with cortisone; actually, hypotension ensued! These results may explain in part the significant and gratifying results of Wilkins (20), Assali & Suyemoto (40, 118), and Finnerty & Sites (119).

One of the first groups of investigators to study hydrazinophthalazine in peripheral vascular disease was that of Smith *et al.* (46), who applied the drug's vasodilating properties in the treatment of patients afflicted with intermittent claudication, phantom stump pain, Buerger's disease, etc. Benefit was obtained without appreciable drops in blood pressure. Under such conditions skin temperatures are also elevated. Although hydrazinophthalazine is effective in the conditions described, other agents as a rule have met with more general acceptance in this regard; these include histamine, nico-

[3] DCA (deoxycorticosterone acetate).

tinic acid, beta-pyridyl carbinol (Roniacol), azapetine (Ilidar), and tolazoline (Priscoline). Side reactions appear with all of these agents and clinical choice depends upon various factors such as age of the patient, nature of the disturbance, associated conditions such as peptic ulcer or hypertension, dose and frequency of administration, route of administration, and cost of the drug.

The chief clinical use of hydrazinophthalazine is in the treatment of hypertension [Wilkins (7); Page (47); Hafkenschiel (48); Schroeder (49); and others]. Here it becomes a very valuable agent despite its early and delayed side reactions [Allen *et al.* (50)]. The early undesirable reactions include mild to severe headaches, flushing, and tachycardia. These are practically all eliminated or prevented by the previous or concomitant administration of antihistamines (50), ganglionic blocking agents (49), or forms of Rauwolfia (50, 51). Also, the use of small initial dosage with gradual increments usually prevents the onset of headache (107) although tachycardia may persist. The latter is, as a rule, nicely controlled by Rauwolfia in some form (7, 51).

The most important delayed side reactions of hydrazinophthalazine are those of arthralgia of the rheumatoid type and in some cases the appearance of a lupus erythematosus-like syndrome. These delayed reactions have appeared most frequently after relatively high doses such as 600 to 800 mg. or more per day, administered during the course of several months to a year or more. On the other hand, there are a few reports of this syndrome appearing after only a few months of administration of the drug at a dose level of 200 to 400 mg. per day. The potential development of this serious syndrome bears careful watch of the patient as it usually remits, according to Allen (50) and others, upon withdrawal of the medication. Such withdrawal, as a rule, must be exercised with reasonable precautions in order to prevent subsequent rapid onset of hypertension [Schroeder & Morrow (49)]. Therefore, auxiliary therapy in the form of ganglionic blocking agents, or more desirably a preparation of Rauwolfia, is indicated as previously discussed under the section dealing with Rauwolfia and reserpine.

In the event of the rare appearance of the lupus type of syndrome, it may be treated with cortisone or corticotropin according to the experience of Schroeder (52), Dustan *et al.* (53), and others. It would seem that one might expect less frequent appearance of this delayed but serious reaction to hydrazinophthalazine if Rauwolfia in some form is administered simultaneously, thus permitting reduction of the dose of the former drug.

Ganglionic Blocking Agents

Tetraethylammonium chloride (*Etamon*).—Tetraethylammonium chloride was the first drug in this group to have been introduced in the United States. Despite its clinical toxicity, it met with varying degrees of success and was instrumental in promoting the intensive search for better and more active agents. Tetraethylammonium chloride, a chemical long known, serves as an excellent example of the importance of studying completely the pharmacol-

ogy of a new drug with the hope of its application to certain clinical conditions in which control by the autonomic nervous system is known to be disturbed. The pharmacologic studies of Acheson *et al.* (54, 55) and their clinical application by Berry *et al.* (56) to certain peripheral vascular diseases will long remain as classic and pioneering work in the rapidly developing and important field of ganglionic blockade.

Hexamethonium chloride.—Hexamethonium chloride (or other salts such as phosphate, tartrate, bitartrate, bromide, etc.) as a result of early studies of Paton & Zaimis (57) in England and clinical studies in this country by Grimson (58), Finnerty & Freis (59), Freis *et al.* (60), Perry *et al.* (61) and others, soon replaced tetraethylammonium chloride, especially for the treatment of certain types of hypertension. This drug is available under numerous proprietary names (Bistrium, Methium, etc.) in this country both for parenteral and oral administration. There is little doubt that it is a most effective agent for the treatment of neurogenic or essential hypertension but certain of its undesirable actions clinically have led to cautious use by many physicians and complete failure of acceptance by others.

Various schemes of dosage of this drug when administered either parenterally or orally have been designed and advocated, but the average patient apparently can be quite successfully treated orally according to the plans of Grimson (58).

The chief and dangerous side reactions associated with the administration of hexamethonium in any form are those of orthostatic hypotension, blurring of vision, dizziness to the point of syncope, impotence, and constipation. Careful adjustment of dosage is frequently mandatory. Constipation can be controlled best in some patients by mild catharsis in the form of milk of magnesia or other mild laxatives.

An important feature to be kept in mind is that of potentiation of the hypertensive action of epinephrine in the subject under hexamethonium therapy; this potentiation may hold true for most ganglionic blockers. Therefore one should be most cautious when considering the therapeutic use of epinephrine for any indication whatever and in particular for the correction of severe hypotension as induced by ganglionic blockage.

Hexamethonium has been combined quite successfully with other antihypertensive agents by various investigators and this has been discussed previously.

Pentapyrrolidinium (*Ansolysen*).—Pentolinium tartrate was developed in England and was first studied pharmacologically by Wien *et al.* (63) and clinically by Smirk (64) and Maxwell & Campbell (65). Pentolinium is a ganglionic blocking agent which acts like hexamethonium but is effective in lower dosage. Somewhat lessened side reactions, similar to those elicited by hexamethonium, have been claimed however, for this drug. It is in comparatively wide usage in this country at the present time and such usage is supported in part by the studies of several clinical investigators of this country [Freis *et al.* (66); Hoobler (67); Allen *et al.* (50); and others].

Pentolinium is administered preferably by mouth using the schedule of

Smirk for the treatment of hypertension as so well outlined in his excellent article on "Antihypertensive Drugs" (62).

Trimethaphan (*Arfonad*).—Trimethaphan is a recent addition [Randall *et al.* (68)] to the field of ganglionic blocking drugs, as is azomethonium bromide (Pendiomide) (69) although the latter is not available in this country. Trimethaphan is best administered by injection. Although effective in certain hypertensive patients, it seems to be well designed for controlled hypotension during surgery. According to Weeter & Giannini (70) trimethaphan is administered intravenously for controlled hypotension by slow, careful infusion of a 0.1 per cent concentration in dextrose and water. It is rapid in onset of action and of shorter duration than hexamethonium; this constitutes a great advantage in certain cases. Whether trimethaphan will generally replace hexamethonium and other ganglionic blockers in "controlled hypotension" is a moot point at present; indications are that it may in due course.

Chlorisondamine (*Ecolid*).—Because of the relatively high doses of certain ganglionic blocking agents now employed, considerable research has been directed by various laboratories toward the development of a ganglionic blocking agent which is effective in low dosage, is readily and uniformly absorbed from the gastrointestinal tract after oral administration, and which elicits side reactions minimal in number and degree. Recently Plummer *et al.* (71) reported pharmacologic studies of chlorisondamine (Ecolid) (Su-3088) and these results were applied clinically by Grimson *et al.* (72). As a result of these several studies which are still continuing, the following conclusions seem justified: "Chlorisondamine is an orally active ganglionic blocking agent capable of suppressing pressor reflexes, reducing blood pressure in the supine position and producing postural hypotension for 12 or more hours after the ingestion of a small dose, 50 to 100 mg" (72).

If additional experiences justify these conclusions and the preliminary impressions of others (73 to 76), it would seem that a consistent, orally effective drug in small dosage (49) may soon be available for purposes of ganglionic blockade in the treatment of certain hypertensive patients. As yet its value and limitations have not been studied in other clinical conditions associated with sympathetic predominance; it would seem, however, that its markedly prolonged action would not presage its use for "controlled hypotension." It is likewise too early to state whether its sympatholytic effects might be applied to the treatment of peripheral vascular diseases as Berry *et al.* did with tetraethylammonium chloride (56).

The most recent announcement concerning new ganglionic blocking agents effective in low dosage is that of Moyer *et al.* (120) which concerns mecamylamine. Although Moyer has studied it only when combined with reserpine, this new drug, which would seem to be the most potent agent of this type studied to date, is uniformly absorbed after oral ingestion and is prolonged in action.

It is apparent when one considers such side reactions as blurring of vision and constipation that the currently available ganglionic blocking

drugs are not selective in establishing such blockade only in sympathetic ganglia; their pharmacologic activity obviously reaches over to those parasympathetic ganglia associated with those portions of the autonomic nervous system. Were one ever able to develop an agent which would be still more selective for sympathetic blockade with minimal or no effect on the parasympathetic ganglia, one would probably have attained the ideal drug for such use. This is probably too much to hope for in view of the fact that acetylcholine seems to be the chief, if not the only, humoral substance responsible for or associated with transmission of the nerve impulse across the synapse at the pre- post- ganglionic connections. Despite this seeming improbability, however, the search for such selective action proceeds.

Peripherally Acting Sympathetic or Adrenergic Blocking Agents

One of the earliest known antagonists of epinephrine and sympathetic nerve stimulation is yohimbine. Because of its toxicity it seems to be of no practical importance but it justifies the reputation of having stimulated much intensive effort among pharmacologists (27, 28) and chemists to seek a clinically tolerated and effective sympathetic blocking agent. Its use cannot be well justified in clinical medicine today.

Ergot derivatives.—Various members of the ergot family have long been with us and one of chief clinical import is ergotamine tartrate (Gynergen), used so successfully in the treatment of migraine headache. In this condition, however, it would seem that the drug's sympathetic blocking activity would be of value only in the spastic type of migraine, that is, in that patient whose cerebral vessels were functionally spastic because of overactivity of its sympathetic nerve control. As this spastic type of migraine seems to be less prevalent than the congestive type, it would seem that the chief virtue of ergotamine tartrate's value in the relief of migraine headaches would be associated with its well-known, smooth muscle contracting action so characteristic of the ergot family [Graham & Wolff (77)].

More recently, dihydroergot derivatives in the form of dihydroergocornine, dihydroergocristine, and dihydroergokryptine have been made available and have met with varying degrees of success clinically. Although they are capable of producing adrenergic blockade peripherally in the blood vessel, they also exert, according to certain studies of Konzett & Rothlin (78), a central blocking action in the region of the hypothalamus and medulla in that they seem to diminish in varying degrees the outflow of sympathetic impulses from these and other centrally located centers associated with the control of sympathetically innervated blood vessels. When combined in appropriate portions, the preparation is known as Hydergine [Bluntschli & Goetz (79)], which seems to be effective in some hypertensive patients; unfortunately there have been reports [Moister *et al.* (80); Schissel *et al.* (81)] that its initial valuable hypotensive action is not always maintained after oral administration.

Ergotamine tartrate has been used with some degree of success in the

control of exophthalmia associated with hyperthyroidism but since the advent of specific antithyroid agents such as various members of the thiouracil family, the use of ergotamine tartrate is primarily restricted to its quite consistent successful control of congestive migraine headaches.

Tolazoline (*Priscoline*).—Tolazoline has been successfully employed for the last decade or more as a peripheral vasodilator in Raynaud's disease and other conditions associated with sympathetic predominance. Although tolazoline is an anti-adrenergic substance, that is, a sympathetic blocking agent at the myoneural juncture in the blood vessel wall, it would seem that its therapeutic advantage is gained chiefly through its histaminic type of direct action on the smooth muscle of the vessel [Grimson *et al.* (82)]. This drug has been employed successfully by several investigators [Smith *et al.* (83)] and others 84 to 87)] in the treatment of painful spasms associated with the acute phase of poliomyelitis on the basis that such spasms are associated with ischemia due to sympathetic predominance localized in the sympathetic ganglia or spinal sympathetic centers because of "virus insult"; other investigators [Geisler *et al.* (88)] have reported little or no success with this type of therapy and many still resort to the cumbersome and costly procedure of hot pack applications. Tolazoline has been used intravenously or by ipsilateral intracarotid injection with definite success in the acute phases of cerebral vascular accidents, especially of the thrombotic or occlusive type [Alpert (89); Bennett (90)]. The chief undesirable reactions associated with tolazoline therapy include gastric distress in those patients peculiarly susceptible to the gastric secretory stimulating properties of the drug, exacerbation of peptic ulcer (particularly gastric ulcer), hypermotility of the intestinal tract, chilling and goose-pimpling of the skin, and in some patients a sense of palpitation. Tolazoline is of little value in other conditions associated with or due to sympathetic predominance.

Phenoxybenzamine (*Dibenzyline*).—Phenoxybenzamine is a derivative of N,N-dibenzyl-β-chloroethylamine (Dibenamine), the pharmacology of which was extensively studied by Nickerson & Goodman (91). Dibenamine remains a scientific curiosity because of the prolonged sympathetic blockade which it produces. Its toxicity is such that it has never been made available to clinical medicine but one of its derivatives, phenoxybenzamine, is useful as a potent antagonist [Allen *et al.* (92)] of epinephrine and norepinephrine, especially as associated with the diagnosis and treatment of a pheochromocytoma. Its use in peripheral vascular diseases has been reported [Goudwin (93)] but as yet the sparsity of critical reports would indicate a lack of general acceptance by the medical profession to date. Goudwin states: "Dibenzyline produces vasodilation of the skin. Its action may persist for two or three days but hypotension, nervous stimulation and the necessity of parenteral administration are serious disadvantages." It would seem, however, that this drug is of sufficient value to warrant thorough clinical trials, alone or combined with less potent agents, in conditions requiring adrenergic blockade or sympatholysis.

Piperoxan (*Benodaine*).—The use of this French discovery by Fourneau

(94) is primarily restricted to the detection of a pheochromocytoma. Numerous reports are available indicating the value of piperoxan in this situation [Emlet *et al.* (95); Goldenberg *et al.* (96); Soffer (97)]. Although piperoxan is a sympathetic blocking agent, it has the disturbing property of analepsis or stimulation of the central nervous system, and convulsions following its use have appeared, according to the literature. For this reason it must be used with reasonable degrees of precaution and with emergency anticonvulsant therapy available in the event that such seizures should follow its intravenous use.

Phentolamine (*Regitine*).—This compound is related to tolazoline in that both are imidazolines, or, in other words, compounds somewhat related to histamine. Phentolamine, however, is a more potent sympathetic blocking agent than tolazoline, piperoxan, dibenamine, or phenoxybenzamine. A smaller dose is required for the average patient in whom the drug is used for the detection of a pheochromocytoma [Emlet *et al.* (95); Roth *et al.* (98); Iseri *et al.* (99)]. In comparison with piperoxan, it seems (97) that phentolamine is more easily used, especially in office practice; its action is consistent and prolonged, and it is not endowed with the convulsive properties associated with piperoxan. It is of genuine interest, however, to observe as Crumpton (100) did that either phentolamine or piperoxan may sometimes substitute for the other in the event that one fails. It is now common practice to employ piperoxan as a confirmatory test of phentolamine (97). Of especial interest is the fact that on rare occasions, as observed by Bannon & Allen (101), both phentolamine and piperoxan might fail in their capacity to detect a pheochromocytoma, whereas phenoxybenzamine may still be effective. The same might be expected occasionally of other adrenergic blocking agents in various sequences.

The adrenergic blocking or antisympathetic action of the stronger members of this group of drugs becomes of great value in those patients harboring a pheochromocytoma who respond most dramatically and dangerously to the hypertensive effects of intravenously administered histamine. In such cases immediate use of piperoxan, dihydroergocornine (102), phenoxybenzamine, azapetine, or phentolamine may constitute a life saving procedure.

These strong peripheral antagonists of the sympathetic nervous system have been used in essential hypertension and peripheral vascular diseases such as Raynaud's or Buerger's disease but with only varying degrees of success. Blair & Yeager (103), for example, have reported favorably on the use of phentolamine orally in two cases of thromboangiitis obliterans and a case of immersion foot but conclude that the drug "is probably of little value in the treatment of hypertension."

In contrast to his favorable results with tolazoline (83), Smith reports (104) that phentolamine is of no value in relieving pain associated with the acute phase of poliomyelitis; this indeed seems paradoxical in view of its antisympathetic action which is stronger than that of tolazoline.

Whether piperoxan, phenoxybenzamine, phentolamine and other similarly acting sympatholytic agents will ever become of more general value in a

greater variety of conditions associated with sympathetic predominance remains to be seen; perhaps by combining with these drugs some other important agent like reserpine acting elsewhere in sympathetic pathways, their therapeutic value may become enhanced.

Azapetine (*Ilidar*).—This potent sympathetic blocking agent, as studied by Randall & Smith (105), is the most recent introduction in this field. It has been reported by Green & Dubose (106) to be of value in vasospastic disorders, postphlebitic syndrome, thromboangiitis, and arteriosclerosis. Its ability to act like piperoxan or phentolamine in the detection of a pheochromocytoma as yet has not been sufficiently established (108).

Although most of these anti-adrenergic substances are quite well-absorbed after oral administration (99), they frequently produce serious side reactions, one of them being tachycardia. If this could be eliminated or corrected, some of these drugs might lend themselves to a wider range of therapeutic use (109).

It is unfortunate that the peripherally acting sympathetic blocking agents cited above are not capable of exercising such pharmacologic activity throughout the entire body; if they could, they would obviously be much more valuable in hypertension and in other conditions associated with sympathetic predominance. To be sure, such a statement would hold true only if associated, or as yet undetermined side reactions, were minimal. On the other hand, the varying degrees of activity of these compounds permit the physician to select to some extent the drug to suit his patient. It is to be hoped that in due course other agents of this type will be developed, permitting wider and more specific application clinically, but already we have agents available which, in the minds of some, may substitute for peripheral neurectomies, as for example in Raynaud's spasm and selected types of hypertension.

General Comments

Sympathetic dominance can be ameliorated safely in patients through well-chosen prescription by the physician. Available today are drugs known as sympathetic depressants, sympatholytics, or anti-adrenergic agents; some act centrally, others at the sympathetic ganglia, or still more peripherally at the end organ under sympathetic control. Appropriate selection of either single agents or combinations of those which exert suppressive actions in different areas of the central or autonomic nervous system may result not only in synergistic and potentiating effects but also in the relief or avoidance (109) of certain side reactions.

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KIDNEY FUNCTION DURING ANESTHESIA[1,2]

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The kidney has many important functions in the maintenance of health. It may induce widespread, harmful effects when it is diseased. The causes of derangement in kidney function are multiple and include intrinsic renal disease, cardiovascular diseases, change of posture, exercise, venous engorgement, anoxia, and a variety of "stresses." Among these are the effects of the anesthetic agents and narcotic drugs. This review will deal with the adjustments of renal activity found in anesthetized states and will attempt to interpret mechanisms and their clinical meanings.

Effects of Narcotics

It is common practice to prescribe a narcotic for sedation prior to induction of anesthesia. Apart from the effects on other systems, it has been known for some time that morphine causes oliguria (1, 2) in normal dogs. Large doses were required before an effect on glomerular filtration rate (GFR) or renal blood flow (RBF) was observed in the dog with diabetes insipidus (3). In eight surgical patients, Habif *et al.* (4) demonstrated that meperidine, in therapeutic doses, depressed RBF 24 to 50 per cent and GFR 24 to 45 per cent below control values. The urine flow always decreased, especially during a water diuresis. The urinary concentrations of sodium, potassium, and chloride ions were increased but the total electrolyte output diminished. The reduction of potassium excretion paralleled that of GFR whereas the excretion of sodium and chloride was reduced more than the GFR.

The mechanism of the antidiuretic action of morphine was studied by several groups of investigators. It was concluded by de Bodo & Sweet that morphine stimulates the hypothalamo-hypophyseal system, thus liberating the antidiuretic hormone (2, 5, 6). They found, in dogs, that antidiuresis occurred only when a functioning neurohypophysis was present; morphine did not inhibit water diuresis in animals with diabetes insipidus. On the other hand, Handley & Keller (3) demonstrated that morphine induced antidiuresis even in dogs with diabetes insipidus. They further showed that this scanty urine had an antidiuretic effect when injected into a second dog. They concluded that morphine antidiuresis is due to the reduction of the number of functioning nephrons as well as the release of antidiuretic hormone. Handley & Moyer presented evidence to suggest that at least part

[1] The survey of literature pertaining to this review was completed in May, 1955.

[2] The authors wish to express their appreciation to Mr. Erich Meyerhoff of the medical library, Columbia University, for his valuable assistance.

of the immediate renal effect of morphine is secondary to hemodynamic changes (7). When arterial pressure fell after morphine was given, the decrease of RBF and GFR was more marked than in those animals in whom the arterial pressure was not depressed. To some extent this finding corresponds to the observation of Habif *et al.* in man with meperidine (4).

An interesting study of the mechanism of morphine antidiuresis is that of Duke, Pickford & Watt (8). In dogs given chloralose, they were able to induce an antidiuretic effect by injecting 4 to 32 μg. of morphine in 1/500 ml. of normal saline locally into the supraoptic nucleus during water diuresis. Section of the supraoptic tract abolished the morphine antidiuresis. The antidiuretic effect of morphine persisted after adrenalectomy on one side and suprarenal denervation of the other side. They concluded that morphine induced antidiuresis by its direct action on the supraoptic cells, causing the release of antidiuretic hormone (ADH) from the posterior pituitary gland. This work confirmed the findings of de Bodo. They further concluded that release of epinephrine is not a factor in the production of antidiuresis and that the effect of morphine is not related to its anticholinesterase activity. N-allyl-normorphine is devoid of antidiuretic activity but antagonizes the antidiuretic action of morphine (9).

General Anesthesia

The suppression of renal function by general anesthetics was first described in 1905 by Pringle (10). He found that there was oliguria and depression of sodium and nitrogen excretion in man during ether anesthesia. Renewed interest in the behavior of the kidney during anesthesia developed with the availability of quantitative measurements of discrete renal functions. It is now well established in recent investigations that all general anesthetic agents significantly diminish renal plasma flow, glomerular filtration rate, and water and electrolyte excretion if there is sufficient depth of anesthesia. This is true in animals and in man (4, 11 to 14).

There are quantitative differences among the results of the various investigators which may be due to variations in depth of anesthesia, differences in prior hydration, or differences in the use of osmotic materials for the measurement of kidney function. In any event, the depression of renal function without significant change in arterial pressure indicates that intrarenal vasoconstriction occurred and may be profound indeed.

Surgical operations of various magnitude did not further aggravate these changes in the absence of shock or serious hemorrhage. Upon termination of anesthesia the various kidney functions had a tendency to return toward control levels within a short time (4).

Effect on electrolytes.—During general anesthesia with cyclopropane, ether, or thiopental and nitrous oxide-oxygen, there was extensive retention of sodium and chloride. The effect on potassium was much less predictable (4).

Strauss, Rosenbaum & Nelson (15) studied the effect of alcohol on renal excretion of water and electrolytes in man. They found that marked diuresis

occurred which resulted in hypertonicity of the plasma. The GFR was not changed and ingestion of water did not prevent the loss of water in excess of electrolytes. Rubini *et al.* (16) conducted similar clinical investigations. In well-hydrated subjects the administration of 120 ml. of 110 proof Bourbon whiskey resulted in slight inebriation. The mean blood alcohol concentration reached a peak of 110 mg. per 100 ml. within 90 min. and gradually dropped to 25 to 50 mg. three hours later. There was a three- to ten-fold increase in the volume of urine. The maximal water clearance corresponded to the peak of blood alcohol concentration. The increase of urine volume was associated with a decreased excretion of sodium, potassium, and chloride. The plasma pH decreased 0.13 ± 0.03 units with a fall in plasma bicarbonate concentration and a decrease in pCO_2. Kleeman *et al.* believe that the rise in water excretion is caused by inhibition of the release of antidiuretic hormone (17).

The interpretation of these alterations in renal function during anesthesia has been beset with many difficulties. Some of these difficulties are the result of dealing with indirect evidence, some the result of trying to understand the function of one organ in the presence of continual change in the behavior of other organs which influence the kidney. There is also a scarcity of pertinent information during some of the states associated with general narcosis.

It is unlikely that the changes in RBF and GFR are due to direct action of anesthetic agents. These changes are readily reversed at the end of the anesthetic period when the concentration of active anesthetic drug could not have been altered significantly (4).

It is possible that the changes in renal function are reflections of a widespread alteration of hemodynamic activity during anesthesia. It has been shown that a significant decrease in arterial pressure or cardiac output is associated with a diminution of RBF, GFR and electrolyte excretion. Shipley & Study (18, 19) observed, in anesthetized dogs, that the RBF and GFR remained relatively independent of arterial pressure changes within the range of 80 to 180 mm. Hg. However, below 80 mm. Hg a fall in arterial pressure resulted in a decline of RBF. Urine flow began at 60 mm. Hg and increased until the arterial pressure was elevated to a high level when the urine volume became 25 to 70 per cent of the GFR. They believed that the increased intrarenal pressure associated with high arterial pressure was responsible for the large urine flow by diminishing the transfer of filtrate through the tubular cells. Conversely a low arterial pressure and low intrarenal pressure favored increased tubular reabsorption and a reduction of urine flow.

A reduction in GFR may also promote tubular reabsorption of solids and water and result in diminished electrolyte and water excretion. Thompson & Pitts (20) lowered the renal arterial pressure with a balloon placed in the aorta of anesthetized dogs. They showed that the excretion of sodium and water was markedly diminished and the percentage of filtrate reabsorbed was increased when RBF and GFR were reduced. Since adrenalectomy,

pituitary stalk section, or sympathetic denervation of the kidney did not change the renal responses, they concluded that these changes were neither neural nor humoral in origin. Leaf *et al.* (21) obtained similar results in unanesthetized dogs by graded compression of the renal artery with a pneumatic cuff. They observed that the reduction in urine flow and total solid excretion was proportional to the decrease in GFR. Berne & Levy (22 to 24) found, in anesthetized dogs, that the reduction of cardiac output by pulmonary arterial constriction resulted in diminution of the RBF, GFR, urine output, and sodium excretion. Quantitatively renal denervation did not alter these responses. They thought, therefore, that the efferent arteriolar constriction was not neurogenic but probably humoral in origin. The identity of this hormone remains obscure.

An increase in the renal venous pressure influenced renal function. Selkurt, Hall, & Spencer (25, 26) observed that graded, partial obstruction of the renal vein resulted in decreases of RBF and GFR in the anesthetized dog. The sodium excretion and urine volume were decreased proportionately so that the concentration of urinary sodium was not altered. Congestion of other venous beds also produced changes in renal hemodynamics and electrolyte excretion. The RBF, GFR, water, and electrolyte excretion were depressed upon application of a tourniquet to the limbs or obstruction of the superior or inferior venae cavae, above or below the renal veins. Fitzhugh *et al.* (27) found in man that the cardiac output was diminished when a tourniquet was applied to the legs. They suggested that the reduced cardiac output was due to a decrease in effective circulating blood volume and was responsible for the fall in RBF and possibly GFR. Infusion of 1000 ml. of normal saline during venous congestion increased the cardiac ouput and elevated the RBF and GFR to control values. However, the urine volume remained depressed. Farber *et al.* (28, 29) showed that balloon-induced obstruction of the inferior vena cava in man depressed renal function for approximately 20 min., while the water and electrolyte excretion remained at low levels or decreased further. They concluded that renal hemodynamic effects may have contributed to the initial change in water and electrolyte excretion but are not necessary for its continuance. The mechanism for the prolonged antidiuresis was not clear to these authors. Wilkins, Judson and their co-workers (30, 31, 32) observed that the changes in renal function during venous congestion of limbs were essentially similar in normotensive and hypertensive subjects both before and after splanchnicectomy, suggesting that neural impulses did not account for the renal effects. They showed that changes in renal function occurred only when there was a decrease in the cardiac output and could be prevented by blood transfusion. They also suggested that antidiuresis is probably mediated through the posterior pituitary antidiuretic hormone. In patients with diabetes insipidus, venous congestion produced the usual changes in RBF, GFR, and electrolyte excretion but only a slight decrease in the urine volume.

In view of the evidence presented, it is apparent that changes of a general hemodynamic nature can produce alterations of renal hemodynamic

function and water and electrolyte excretion. In well-conducted anesthesia, cardiac output, peripheral resistance, blood flow, as well as the distribution of blood in various segments of the vascular system, change appreciably. In addition to the effects of anesthetic drugs, the conduct of surgical anesthesia in man presents other complicating factors such as depth of anesthesia, surgical trauma, hemorrhage, change of respiratory mechanics, anoxia, acidosis, and pre-existing "medical diseases." These also contribute to the changes in over-all hemodynamic behavior.

Some hemodynamic effects of general anesthesia.—During light ether anesthesia there was an increase in cardiac output, a decrease in peripheral resistance, and sometimes a decrease of arterial pressure (33, 34). These changes are presumably the result of sympathetic activation (35, 36). Light cyclopropane anesthesia, on the other hand, caused a decrease in cardiac output and an increase in total peripheral resistance. There was generally an elevation of arterial pressure (37, 38). Thiopental caused no significant change in cardiac output in light narcosis. Both cardiac output and total peripheral resistance decreased during surgical anesthesia. The intrathoracic blood volume was reduced (39). According to Lee *et al.* (14) and Lynn & Shackman (40) the blood flow through the skin and muscle of the extremities was increased in light anesthesia. During prolonged or deep anesthesia the skin and muscle blood flows were reduced below control values. The splanchnic and renal blood flows were also reduced. The venous pressure was increased with cyclopropane (38) and ether anesthesia (33) and decreased with thiopental anesthesia (41).

There is, therefore, a redistribution of blood flow even in light anesthesia consisting of vasodilatation in the skin and muscle with some vasoconstriction in the renal and the splanchnic vascular beds. In deep anesthesia the total peripheral resistance markedly increased and was associated with a reduction of blood flow through both the skin and muscle and the splanchnic and renal vascular beds. Except for ether anesthesia the mechanism of these changes is poorly understood. The fact that renal and splanchnic vasoconstriction regularly occurred, despite variable changes of cardiac output and arterial pressure, indicates that these hemodynamic changes may contribute to the alteration in renal function but that other unknown physiological factors must also be involved. The mechanisms responsible for these vascular changes are of great importance even though understanding of them is limited. The issue of whether or not the autonomic nervous system is important in causing renal functional changes during general anesthesia has not been settled. Much evidence is accumulating that suggests such an influence may be of physiological importance. However, further studies in anesthetized man appear necessary to settle some of the areas of conflicting evidence.

It will be recalled that data also exist suggesting that the changes in renal function are mediated via hormones. These effects are not so well known nor are the arguments as pointed as in the case of the neural mechanisms. Some comment on possible hormonal effects is, therefore necessary.

Activity of the pituitary-adrenal system is increased during anesthesia and operation. Sandberg *et al.* (42) found that the plasma level of 17-hydroxycorticosteroids in a group of surgical patients was elevated following the induction of general anesthesia during and after surgery. Tyler *et al.* (43) suggested that this increased plasma level of 17-hydroxycorticosteroids after surgery was the result of increased adrenal secretion of these steroids and impaired hepatic removal. The stimulation of the pituitary-adrenal system by the stress of anesthesia and operation could possibly explain the postoperative sodium and water retention and increased excretion of potassium. Indeed it was shown by Hardy (44) in man that the eosinopenia after surgical procedures coincided with the depression of urinary output. The effects of exogenous ACTH and cortisone during general anesthesia are unknown.

It is known that ether anesthesia causes an increase in circulating epinephrine (45). Recently Brewster *et al.* (46) demonstrated that the secretion of adrenal medullary hormone was responsible for the increase in cardiac output, hyperglycemia, and accumulation of lactic acid in the plasma during etherization. After epidural block, sympathectomy, or adrenalectomy these responses to ether were not observed. Elmes & Jefferson (47) showed that epinephrine was lost from the adrenal gland during cyclopropane anesthesia and a slight hyperglycemia may occur. The effects of adrenal medullary hormones on renal hemodynamics and electrolyte and water excretion bear some resemblance to those observed during general anesthesia. The renal responses to epinephrine and norepinephrine have been studied in animals and in man. Within certain dose ranges the results were in good agreement (48 to 53). Both epinephrine and norepinephrine produced marked renal vasoconstriction, particularly of the efferent arterioles. The RBF was always reduced. The GFR was decreased or unchanged but the filtration fraction (FF) was usually elevated. The excretion of sodium, chloride, and potassium was depressed. Jacobson *et al.* (48) suggested that the reduced electrolyte excretion was probably due to (*a*) decreased filtered load, (*b*) increased rate of reabsorption from the tubules, or (*c*) decreased velocity of flow in the tubular lumen, or from all these three factors. Smythe *et al.* (49) raised the possibility of stimulation of the anterior pituitary-adrenocortical system by epinephrine or norepinephrine. However, they recognized that, contrary to their findings, this action would tend to promote instead of depress the excretion of potassium. Furthermore, Duncan *et al.* (54) showed that chronic administration of adrenal medullary hormones to man constitutes no more than a very weak stimulus to adrenocortical activity. Sandberg *et al.* (55) found that epinephrine had no effect on adrenocortical activity nor the metabolism of corticosteroids. Evidence was presented by Eränkö *et al.* (56) and Dearborn & Lasagna (57) to suggest that the adrenal medullary hormones may induce antidiuresis by the stimulation of posterior pituitary antidiuretic hormones. They also showed that the prolonged antidiuresis of epinephrine did not occur in dogs whose hypothalamo-hypophyseal system was surgically damaged. It appeared probable that adrenal medullary hormones can cause antidiuresis through (*a*) local

vascular constriction and a subsequent decrease of filtered load, and (*b*) release of antidiuretic hormones from the hypothalamo-hypophyseal system.

Although direct evidence is lacking, comparison of alterations in renal function during general anesthesia with those following the administration of epinephrine or norepinephrine showed certain parallels. It is, therefore, possible that the changes in renal function during anesthesia are in part due to the stimulation of the adrenal medulla by the anesthetic agents.

The role of the antidiuretic hormone of the posterior pituitary gland in the production of antidiuresis during anesthesia is difficult to ascertain. The secretion of ADH could be increased as a direct effect of the anesthetic agent or indirectly through the increased activity of the adrenal medulla. Except for barbiturate anesthesia direct evidence in this respect is lacking (58, 59).

In unanesthetized animals and man, the kidney compensates for metabolic or respiratory acidosis by changes in the excretion of electrolytes and the titratable acid of the urine. In fact, one of the most important functions of the kidney is the regulation of the acid-base balance of the body fluids (60 to 64). Acidosis, respiratory or metabolic, sometimes of a marked degree, occurs during general anesthesia. Unfortunately, no data concerning the renal response to acidosis during anesthesia are available. Since the renal hemodynamic and excretory functions are depressed to such an extent by general anesthesia, it seems reasonable to assume that the compensatory capacity of the kidney to correct disturbances of acid-base equilibrium is markedly reduced during general anesthesia.

During anesthesia, anoxia may occur from respiratory depression or airway obstruction. However, satisfactory data concerning the influence of anoxia on renal function during anesthesia are not available. In unanesthetized man, Berger found an increase in RBF but the GFR did not change appreciably with arterial blood pO_2 as low as 50 mm. Hg. The urine flow and sodium, chloride, and potassium excretion increased (65). Earlier Stickney *et al.* (66) observed that the urine flow was augmented during moderate anoxia (9 vol. per cent O_2 in inspired air) in the anesthetized dog. Selkurt (67, 68) produced local renal anoxia by perfusing the kidney with venous blood. He showed that the RBF increased an average of 22 per cent after perfusion of blood with an average blood O_2 content of 10.7 vol. per cent. The renal vascular resistance showed a typical reduction. The glomerular filtration decreased 10 per cent on the average. There was a decreased filtration fraction suggesting efferent arteriolar vasodilatation. The excretion of water, sodium, and potassium increased, possibly indicating that there was slight impairment of the tubular reabsorptive processes (68). Axelrod & Pitts (69) studied the effect of anoxia on renal tubular function in unanesthetized dogs and man. They found that the inhalation of anoxic mixtures produced little effect. It was their conclusion that the mechanisms for changes in renal function during chronic hypoxia are extra-renal in origin. Dole *et al.* showed, when the arterial O_2 content is low, that the O_2 uptake of kidney remains the same as under normal conditions (70).

Spinal Anesthesia

The studies of the effects of spinal anesthesia on renal hemodynamics and excretory function are in poor agreement. This is not too surprising since the conditions of the experiments were so variable in the height of blockade, type of subject, and duration of the period of observation.

In order to evaluate the experimental findings, the alterations in general hemodynamics due to spinal anesthesia must first be examined. There is frequently an immediate fall of arterial pressure during high subarachnoid blockade. Many theories concerning the cause of the hypotension have been advanced. From the available evidence the hypotension can probably be attributed to (*a*) postarteriolar stasis and consequent reduced cardiac output, and (*b*) loss of arteriolar tone from sympathetic blockade. Earlier studies of high spinal block in man by Smith, Rovenstine and their co-workers (71, 72) indicated that the cardiac output decreased and the total peripheral resistance was relatively unchanged in unoperated, unmedicated subjects. The venous pressure fell consistently and was independent of arterial pressure changes (73). The venous circulation time was also increased (74). It was concluded that stagnation in the post-arteriolar bed was the primary cause of hypotension during spinal anesthesia (75).

Recently a complete survey of the hemodynamic changes during spinal anesthesia in man was undertaken by Sancetta, Lynn and their co-workers (76, 77). According to these authors the important changes associated with hypotension were a reduction of cardiac output, stroke volume, right atrial pressure, pulmonary arterial pressure, and total peripheral resistance. The intrathoracic blood volume was also decreased. The arterial oxygen content was not significantly reduced but the arterio-venous oxygen difference was increased. These changes were more marked when the sensory anesthesia reached a level higher than T_4. In the periphery it was found that spinal anesthesia below T_4 produced an increase in pulse volume in the toe, and a decrease in pulse volume and blood flow in the finger. During spinal anesthesia above T_4 there was an increase in pulse volume in both the finger and toe. This confirmed the earlier findings of Neumann *et al.* (78). The increased flow through the anesthetized area indicated that there was dilatation due to blockade of sympathetic vasoconstrictors. The reduced atrial pressure and stroke volume in the face of reduced total peripheral resistance could mean nothing other than reduced venous return. Concerning the reduction of venous return there are again controversial opinions. Muscular relaxation was thought to be responsible but Sarnoff *et al.* (79) and Assali & Prystowsky (80) showed that the fall in arterial pressure and cardiac output occurred without motor paralysis.

These studies indicate that hypotension may be due to multiple factors. The level of anesthesia is certainly important since the vascular bed in the unanesthetized area can and does compensate for the loss of vascular tone in the anesthetized part of the body. Therefore, regional vascular resistance may change but the total peripheral resistance may or may not change,

depending upon the area available for compensatory vasoconstriction.

The hemodynamic changes in the renal and splanchnic beds during spinal anesthesia were investigated. Smith *et al.* (71) found that renal hemodynamics were not significantly altered. They concluded that renal vessels do not depend upon sympathetic impulses for normal tone. However, Corcoran, Taylor & Page (81, 82) reported that spinal anesthesia at a level of T_{5-6} in man increased the RBF with a reduction of both afferent and efferent arteriolar resistance. While their investigation was primarily performed on hypertensive subjects, normotensive subjects showed qualitatively similar changes. The increase of RBF in the face of a reduced cardiac output would indicate a loss of vascular tone in the renal bed. Contrariwise, Assali *et al.* (83, 84) observed in the normal pregnant woman, in whom the compensatory mechanisms are supposedly less efficient, that the RBF and GFR decreased markedly with spinal anesthesia. Mueller & Lynn (85) and their co-workers found that the estimated hepatic blood flow was also reduced with high or low spinal anesthesia in man. Mueller *et al.* did not demonstrate any significant or consistent change in the splanchnic vascular resistance; Assali *et al.* (84, 86, 87) showed an actual increase in the renal vascular resistance. They assumed that a humoral agent was responsible for the active compensatory renal vasoconstriction they observed and suggested that epinephrine or norepinephrine might be the agent. The clarification of these conflicting data awaits future study.

Water and electrolyte excretion during spinal anesthesia were also investigated by Assali *et al.* (84). It was found that the urine flow decreased. The sodium and chloride excretion was also reduced but potassium excretion varied. The antidiuresis was more marked with hypotension but it always outlasted the hypotension. The RBF and GFR were either unchanged or reduced during the antidiuresis. They suggested that the reduced cardiac output was partly responsible for the reduced RBF and GFR. The reduced GFR would explain the inhibition of water diuresis but, as the inhibition of diuresis outlasted the hypotension and sometimes occurred in the absence of RBF and GFR changes, it seemed possible that pitressin secretion through an unknown mechanism might play a part in the production of antidiuresis during spinal anesthesia. Again the question is open for further investigation.

The differences in experimental results and, therefore, in interpretations, are difficult to reconcile. One may offer one explanation. When a subject is normal, unmedicated, and disturbed to the least possible degree, minimal changes in renal function occur with spinal anesthesia. Change in position, medication, changes in ventilation, even forceful suprapubic pressure to empty the urinary bladder may precipitate a fall in arterial pressure. Once the blood pressure falls in the face of sympathetic blockade, a chain of events is set into motion which can account for many of the reported observations. It must be remembered that these attempts at explaining the differences are speculative and that more must be learned. It is also necessary to point out

that the circumstances of clinical surgery during high spinal anesthesia lead to hypotension unless vasopressor treatment or prophylaxis is employed. In this respect, there is no conflict in the thoughts of clinical anesthesiologists.

Summary

An attempt has been made to present the alterations in discrete renal functions associated with the administration of anesthetic and narcotic agents. It was demonstrated that renal function is profoundly influenced by the events occurring in the anesthetized state. These effects are, in the main, reversible, but of considerable physiological and clinical importance.

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RADIOACTIVITY

INJURY AND RECOVERY FROM IONIZING RADIATION EXPOSURE[1,2]

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Investigation into the nature of the biological effect of ionizing radiations in animals and man has developed into an extensive field. Critical analysis of the combined material demands, initially, an appreciation of the dynamic nature of the subtle injury caused by the ionization process as well as inquiry into the specific biochemical events which multiply into a variety of physiological dysfunctions which eventually result in permanent injury or, with higher doses, death of the animal. Very little is known concerning the specific nature of the ionization process and how it produces those chemical changes which develop into the well-known picture of radiation injury. Conjectures based upon studies of the ionization of water into combinations of H and OH radicals reacting with acceptors in the medium, the possible formation of H_2O_2 or other factors with oxidizing potential, molecular dissociation, or possible toxic factors are difficult to assay in complex biological systems. Studies on the specific alteration of the process by the protective action of sulfhydryl-containing compounds, albumin and other proteins, alcohols, glycols, and oxygen tension only partially explain how such small energy quanta can produce such marked overall cellular damage during a latent period following which physiologic injury is manifest.

The true nature of the process of radiation injury, particularly in mammals, continues to be confused in the scientific mind. Much of this arises from the lack of certain simple appreciations. In whole body radiation with which we are primarily concerned, all tissues receive dosages of radiation of varying amounts depending on the physical factors of the radiation. The cells in the tissues of these animals are altered depending on specific sensitivity. The physiologic effect seen depends upon the sum of the changes occurring in individual tissues. However, it is important to consider that in many species (mouse and guinea pig) certain organs are of much greater importance (more critical) than in others. This is particularly significant in comparing mouse and rat with dog or man. Another factor which is obviously neglected is the appreciation of the nature of repair processes which follow phases of initial injury. Particular substances which may be produced in excess in one phase of the radiation syndrome may be in critical short supply

[1] The survey of literature pertaining to this review was completed in August, 1955.

[2] Some of the work cited in this paper was performed under contract with the United States Atomic Energy Commission at the University of Rochester Atomic Energy Project, Rochester, New York.

in another phase. If one is interested in prophylaxis, therapy, or correction of the radiation effect, he must appreciate the fact that, with a "chain reaction" such as is initiated by radiation injury, certain imbalances may not be corrected by normal homeostatic mechanisms. Studies of the dynamic mechanisms of such control are inadequate, partially due to the lack of good methodology. Much is known of the damaging effects but little of the regenerative ones.

Another factor which is not generally appreciated is that the overwhelming lymphocytic, bone marrow, and intestinal injury with their deleterious consequences of infection, hemorrhage, and anemia completely masks the much more subtle changes which occur in other cells and tissues. Animals which survive large doses of radiation because of the protective action of certain sulfhydryl derivatives, anoxia, or specific therapy with spleen or marrow homogenates may die a short time later from unknown causes. If premature aging from chronic radiation injury is identical with true aging, is it not possible that cells of the bone marrow and gut, which continuously replace themselves through life, actually do not age proportionally to those elsewhere in the body? The understanding of the processes of aging will undoubtedly be promoted considerably by studies of the chronic effects of ionizing radiations.

In this review certain developments which have occurred in the past two years will be evaluated in an attempt to create a more complete understanding of the radiation syndrome.

Concepts of Cellular Damage

Several excellent analyses of this complex subject have been developed in which the concepts related to the initiation and development of damaging effects to cells by ionizing irradiation are reviewed. Gray (1) presents an analysis of the effects of decomposition of water, peroxide formation, oxygen concentration, enzymic sensitivity, and the formation of reducing radicals in test systems. In another review certain characteristics of the biological damage from ionization are discussed and the present state of the problem is appraised (2). Patt (3) presents a development of the present state of knowledge of the varied factors entering the radiation reaction and concludes that no obvious common denominator exists to account for differential sensitivity of the effect of radiation on cells and tissues. The environmental factors which undoubtedly influence the sensitivity of the reaction are amply analyzed. Not only may oxygen play a part in the initial reaction, but the variety of reactions indicates that it also modifies the nature of chemical intermediates as well as other secondary reactions.

Gray *et al.* (4), in noting that sensitivity of tumor cells is greater when radiated in a well-oxygenated medium, suggest that the effectiveness of clinical radiation may be improved if patients were breathing oxygen at the time of treatment. Patt (5) reviews completely the literature on the chemical and physiological effects on mammalian systems over the previous three year period.

As will be demonstrated throughout this review, information related to successful prevention and treatment by the clinician of injury due to ionizing radiation must depend on the prevention or modification of the many intracellular changes which occur following exposure. It is very apparent that the observed changes are more qualitative than quantitative in nature and also that observations made on one tissue can not necessarily be extended to others.

Recent observations on the chemical effects observed in radiated animals not only consider the accepted fact that nucleoprotein metabolism is definitely altered in certain systems but have progressed into investigation of other intracellular and tissue abnormalities. A marked increase in acid DNAase 24 to 48 hr. after irradiation was found, with maximum response at 200 r (6). Spleen and thymus of rats and mice show detectable increases in the enzymic activity of adenosine triphosphocylidase and 5-nucleotidase as early as three hours after exposure, the total change being dose dependent between 25 and 400 r for mice and 100 to 400 r for rats (7). Changes were reversible depending on dosage, lethal amounts producing irreversible change. Harrington & Lavik (8), by analyses of the incorporation of labeled precursors into deoxyribonucleic acid (DNA) following 100 r whole body irradiation to rats, found consistent inhibition of P^{32} into DNA phosphorus, of orotic acid-2-C^{14} into DNA pyrimidines, and of sodium formate-C^{14} into DNA guanine. Incorporation of adenine 8-C^{14} into DNA purine, and formate-C^{14} into DNA thymine or adenine was not altered. These observations extend previous findings of the variation in response in nucleic acid metabolism.

Other studies of enzymic activity indicate a dose dependent increase in the tryptophane perioxidase-oxidase system of rat liver in normal but not adrenalectomized rats (9). Also serum proteolytic and antiproteolytic activities were altered following exposure of guinea pigs and humans to radiation (10). Acetylation of sulfanilamide in rats after high level radiation was not impaired (11). Feinstein & Ballin (12) describe increase in activity of one of three cathepsins in liver, two of three in kidney, and two of three in the intestine. The destruction of an enzyme inhibitor present in leukocytes is offered as a possible explanation.

Other evidence of alteration in tissue function is the enlargement of the liver in rats associated with increase in water and glycogen content (13). Huang, Almand & Hargan (14) noted no morphological changes in the liver, no significant variation in ability of the liver to inactivate antidiuretic hormone, and no changes in renal function. Hewitt & Hayes (15), studying the lipoprotein metabolism in various species, report alterations in serum levels in rabbit, dog, rat, and mouse which occur at a different time for each species. A large increase in low density lipoprotein precedes death in rabbit, rat, and dog. Phospholipid synthesis and lipid destruction in the liver, spleen, and kidney of the fasted rat showed no significant changes (16). Weinman *et al.* (17) report that with high dose radiation (2500 r) more P^{32} is incorporated into the phospholipids of all cell fractions than in the nonirradiated

animal. This did not occur if the P^{32} was administered 24 hr. postradiation.

Detrick *et al.* (18) demonstrate inhibited glucose absorption in the perfused surviving intestinal segment of the rat, especially within the three to six days postradiation period. Microscopic evidence of morphological recovery did not parallel physiological observations.

As much as a tenfold increase in the amino acid excretion of humans following exposure to 25 to 180 rep whole body irradiation has been reported (19). Individual amino acids varied from two to 20 times normal amounts, the most marked change occurring with hydroxyproline and glycine. Changes occurred as early as 12 hr. after exposure, indicating the rapidity of the reaction, and were observed up to five months after exposure.

White *et al.* (20) indicated that low protein diets result in marked increase in nitrogen excretion largely within the urea fraction. This effect occurs to a lesser extent in animals on a 15 or 20 per cent protein diet. Mason (22), in studies on the dog under fasting conditions or with a low protein normal diet with and without irradiation, observed no difference in urinary nitrogen excretion except for some possible increases in the undetermined fraction which may include the amino acidemia reported by others (19). White *et al.* (23) noted development of cirrhosis of the liver in rats on low protein diet and surviving 450 to 500 r total body exposure. Animals on a high protein diet or amino acid mixture did not develop cirrhosis during the 400-day observation period. The presence of infections within the colony complicates interpretation. Smith & Tyree (24) report studies of the pattern of weight loss and food consumption related to whole body and partial body exposure to x-radiation.

In succeeding sections more information on specific systems will be given. Results indicate that most of the observed physiologic changes are related to damage from acute high level radiation exposure. Thus they may be transient and disappear during the recovery phases. Many are common to disorders seen after other physical, chemical, or nutritional stresses. Modifications of the picture occur following hypoxia (25, 26) or use of a great variety of substances including sulfhydryl-containing compounds (27). Most experiments report effects only on acute injury and repair and not on the development of irreversible damage. It is certain that the specific changes which underly these extremely varied observations can only be explained by knowledge of alterations in cellular physiology which may differ from one cell system to another. Information is urgently needed concerning these alterations as well as those mechanisms of humoral or endocrine nature which tie these systems into the complex mammalian body.

Chemical Factors Modifying the Effect of Radiation

Reviews of the effects of the sulfhydryl-containing compounds all conclude that the mechanism whereby these many compounds protect against irradiation is nonspecific (5, 28, 29). Further evidence is offered by Storaasli, Rosenberg & Weisberger (30) who note that D-cysteine and L-cysteine are

comparable in their ability to reduce the effects of total body irradiation and nitrogen mustard in rats. Since in its normal metabolic pathway D-cysteine must be first converted to L-cysteine in order to participate in protein synthesis, its immediate action is therefore interpreted as nonspecific and unrelated to definite chemical interaction. Salerno & Friedell (31), using small doses of x-radiation before treatment with cysteine followed by massive doses of x-ray, showed that cysteine is more protective against large doses than against small doses. The significant feature of their experiments is that approximately one-third to one-half of the biological effect of the x-radiation, irrespective of the dose in r, is antagonized by a given dose of cysteine. This would certainly explain the limits of protection possible with these compounds so that, with a given species, the maximum protective effect could easily be calculated. This concept does not agree with the recent reports of Doherty & Burnett (32) and Hollander (33) who note protective effects above 950 and 1200 r with the use of S, β aminoethylisothiuronium Br-HBr and S, γ aminopropylisothiuronium Br-HBr. Whether the added protection is attained by the substitutes of the ethyl and propyl groups into these compounds is unknown. It is unfortunate that these experimenters like others report the results over only the 30-day acute period so that the effects of the protection against the development of permanent residuals are unknown. Again, all work was carried out on rats and mice, and did not include other species in which this type of protection may be not beneficial. Since most studies of recovery have been directed toward reaction of lymphocyte, bone marrow, and spleen, it might be argued that the specific protective action is on such systems rather than on all physiological systems of the body. As has been shown by the studies on shielding and postradiation administration of spleen and bone marrow, including homogenates and specific fractions, the recovery of the animal is in a large part related to rapid regeneration of the hematopoietic tissues. Immediate survival of these animals for the 30-day experimental period is achieved following high radiation dosages. However, limited observations on late effects indicate that irreparable damage to other systems of the body may lead to early aging and death. Friedell & Salerno (34) comment on the greater significance of the spleen in radiation sensitivity of the mouse as compared with the rat. In both animals primary depression of the hematopoietic system is the major cause of death, but the spleen is much more important in support of the hematopoietic system in mice than in rats.

Other substances shown to have a modifying effect when administered before the radiation are butyl alcohol (35), carbon monoxide, hydrogen sulfide and potassium cyanide in sublethal concentrations (36), ketones derived from pyrogallol (37), ethyl alcohol and others (38). Interest in the flavinoids continues with the report of protection against injury to capillaries of human nail bed (39) and better tolerance to clinical radiation in 403 patients with malignancy treated with an extract of citrus fruit (40). Hesperidin with or without ascorbic acid did not alter radiation survival in rats and

guinea pigs in this laboratory. All studies use lethality and morphological alteration of cells and tissues as end points. None follows life-time physiological changes as an index of irreversible damage.

The Role of Spleen and Bone Marrow in the Recovery Process

Improvement in survival of mice exposed to LD_{100} dosages of radiation following spleen shielding led Jacobson and co-workers to the observation that implantation of spleens (from normal young mice) within the peritoneal cavity of radiated mice also improved survival. Similar results obtained with homogenates initiated a serious inquiry into the possible existence of a humoral factor or factors present in spleen and possibly other tissues. Such studies were reviewed recently (41, 42). Investigations carried out in the LAF_1 mouse indicate that the factor is nondialyzable, unstable, heat labile, and associated with the nuclear fraction of the cell. It is susceptible to the action of deoxyribonuclease and trypsin but not affected by ribonuclease. The spontaneous decrease in biological activity is apparently retarded by deoxyribonuclease inhibitors such as sodium fluoride, suggesting that the factor is found in a deoxyribonucleic acid-protein complex. The factor is present in spleen and possibly bone marrow but not in preparations of thymus, liver, muscle, or lung. Lack of difference between engorged phenylhydrazine-treated spleens and control spleens suggests that this activity is not associated with erythroid elements. In another study Cole & Ellis (43) note a depression of DNA content of the spleen from 24 hr. postradiation until death. Recovery following injection of spleen homogenate results in a reversal of the DNA depression which precedes favorable change in either body weight or leukocyte count. The important fact that such recovery factors pertain only to the hematopoietic system and only to that of the mouse is not to be ignored. Heterologous spleen extracts fail to protect mice (44). Loutit (45), in a review of the known information, expresses the opinion that much of the evidence of possible humoral factors is equivocal and the possibility of a cellular graft from donor to recipient is not excluded. Of possible importance is the information given by Barnes & Loutit (46) that the recovery factor is not lost when stored in infant spleens in a glycerol serum at $-70°C$ for as long as 83 days.

A similar series of studies have been carried out with injection of suspensions of bone marrow, or implantation of marrow intraperitoneally by Lorenz & Congdon (47). They demonstrated that bone marrow of mouse or rat protect against lethal dosages of x-radiation in the LAF_1 mouse. While homologous bone resulted in marrow formation in the transplant, heterologous bone, while protecting, did not elaborate new marrow at the implantation site. These experiments are presented as evidence of a humoral factor. In rats Cole & Ellis (48) report protection with the nuclear fraction of bone marrow homogenates. In an extensive group of experiments carried out by Brown and co-workers (49) lymphoid tissue recovery in irradiated

C57 BL female mice was used as an assay criterion of the protective factor in mouse bone marrow. Marrow cells enclosed in porous intraperitoneal capsules gave no evidence of elaboration of a humoral regeneration factor while controls injected with marrow produced specific stimulation. Differential centrifugation of mouse bone marrow and spleen showed protection only with the nuclear fraction, which was contaminated with intact cells to a varying degree. Activity was related to age of source material and was highest in 7 to 10 day spleens. Regeneration was noted after marrow injection in splenectomized animals, indicating that presence of spleen is not essential. Pretreatment with phenylhydrazine and turpentine did not enhance the effect. With the exception of fetal liver all other tissues were inactive. Marrow from strain A mice and rats showed no activity. Freezing and lyophilization destroyed the activity. It is encouraging that more accurate indices of regeneration are being developed in place of reliance on the effect on mortality alone. So many extraneous factors such as infection, nutrition, and the like have direct bearing on the mortality results that these may be misleading.

Of related interest are the observations that the effect of whole body irradiation in the rat produces definite depression of the DNA of the spleen while similar dosage to the spleen alone produces insignificant change (50). From this one might conclude that the splenic effect was in part contributed to by reaction elsewhere within the body. Spleen exposures in the shielded animal exhibited less pathologic damage and prevention of the inhibitory effect of the radiation in citrate synthesis. A protective action of rat bone marrow in mice was noted, with 50 per cent survival at 30 days (51). A large percentage of late deaths were observed in these mice. Combined cortisone and bone marrow injections may enhance the protective effect.

It is important to remember that these protective measures are directed specifically toward regeneration of the hematopoietic system in mice and that they act to a lesser degree in rats and guinea pigs. Effects of such recovery factors on long term survival and residual injury have not been adequately studied. Evidence indicates that this hematopoietic factor has varying degrees of potency, and can be stored under special conditions. Demonstration of effectiveness in dogs, monkeys, and man becomes the critical demand.

The Nature of Infection, Hemorrhage, and Anemia in Radiation Injury

Major recent contributions to the knowledge of the role of infection and related injury in whole body radiation exposure consist of summaries of previous work. Bond, Silverman & Cronkite (52) analyze the radiation syndrome and separate it into two general pathological types, the intestinal syndrome occurring after high dosage (1000 to 2500 r) with short survival of approximately four days, and the bone marrow syndrome after lesser

dosage (less than 1000 r) with longer survival. The intestinal syndrome is characterized by severe changes in fluid and electrolyte balance, dehydration and vascular collapse; the bone marrow syndrome, by infection, hemorrhage and anemia. Infection is related to the severe leukopenia and impaired immune responses making local invasion of bacteria possible from any source. Parenteral administration of pathogens results in a similar picture. Control of infection, hemorrhage, and anemia depends principally on marrow restoration. Susceptibility to infection, as analyzed by Shechmeister (53), is related to suppression of hematopoietic tissue, inhibition of antibody production, and alteration of reticulo-endothelial functions, particularly of liver and spleen. Antibodies formed before radiation exposure remain active, while no activity is developed postradiation. Vogel *et al.* (54) report differences in the mortality and infection time in CF1 mice exposed to neutrons and gamma rays. Neutron exposure (175 to 250 rep) resulted in early death and appearance of repair between the fourth and eight days. Gamma rays in the exposure range of 750 to 1300 r produced deaths and maximal repair in approximately 12 to 14 days. Such findings correlate with the observed greater intestinal damage, and its slower repair, produced by neutron as compared with gamma ray exposure.

Hammond (55) summarized the current findings concerning treatment of the radiation syndrome. Most favorable results are obtained in mice with streptomycin, in dogs with chlortetracycline and oxytetracycline. Variation in response is observed as antibiotic-resistant organisms appear. Several investigators demonstrated the resistance of mice receiving spleen or bone marrow homogenates to natural or induced infection. Shechmeister and co-workers (56) note protection of spleen shielded mice x-rayed with 350 r against subsequent infection with *E. coli*. Failure of antibiotic therapy to generally benefit therapy in the rat is puzzling. Administration of hematinic supplements in combination with chlortetracycline or oxytetracycline (so-called stress fortification) improves survival in dogs receiving LD_{80} (550 r) dosage of radiation (57). A beneficial response to antibiotic therapy of fast neutron injury was noted, with significant reduction in mortality in the first 10 days as well as increase in mean survival time (58).

Few significant contributions have been made to the effect of radiation on the immune reaction. It is generally agreed that specific effects include the depression of both active and passive immunity against bacterial and parasitic infections but little effect on acquired immunity to viral infections. Antibody formation is markedly inhibited. Hale & Stoner (59) confirm many previous observations with influenza virus, pneumococcus type III protection, trichinella infection, and tetanus antitoxin production from toxoid. In a series of experiments they utilized the inhibitory effect of radiation on antibody formation and the slow recovery in ability of radiated mice to produce tentanus antitoxin as a means of studying the ability of various tissues to form antibody. By implantation of spleen and lymph tissues from mice immunized with tetanus toxoid into the anterior chamber of the eye of irradiated nonimmunized mice, it was possible to test the antitoxin produc-

tion of these tissues while growing as intracellular transplants. It was noted that spleen and lymph node were capable of producing antitoxin specifically when the radiated host was given a second dose of toxoid intravenously 10 days after transplantation. Similar ability was shown by thymus gland and Peyer's patches. No mention was made of the possible elaboration of a humoral factor by the normal transplant and its effect on antibody production. Such studies seem desirable.

The isolation of a substance from blood plasma named properdin by Pillemer *et al.* (60) has excited the curiosity of many research groups. Suspicion of the existence of a "natural antibody" has been expressed by many investigators working in this and related fields. The reduction in the properdin level of rats following irradiation and the therapeutic benefit of properdin administration have been reported. A recent series of experiments in this laboratory on dogs receiving 594 r whole body irradiation demonstrated a 50 per cent decrease in properdin level two days postirradiation (61). This was paralleled by a decrease in the β-γ globulin fraction as determined by the Jacox method (62). A similar initial reduction in white cell count was associated with lymphocyte reduction. As anticipated with this dosage of radiation, those animals treated with antibiotic (chlortetracycline) showed no significant difference except for a prolongation in survival time. In this experiment it was noted that those substances which are related to immunity, namely properdin, β-γ globulin, and leucocytes diminish in parallel while those substances possibily related to coagulation defect increase. Increases were noted in fibrinogen and mucoprotein, while approaching hemorrhage was predicted by increase in clotting time and sedimentation rate.

Analysis of the hemorrhagic tendency in relation to platelet levels and prothrombin utilization was carried out by Cronkite, Jacobs & Schork (63). At three radiation dosages platelets are less active in promoting prothrombin utilization during marrow aplasia while during marrow regeneration the platelets become more active. The depression may be related to increased plasma lipid antithromboplastins, the recovery to increased size and lability of platelets. Bleeding is better correlated with prolonged depression of platelet levels rather than with a specific critical level.

Stroud, Brues & Summers (64) revive an earlier technique used with some success in rats and dogs in their study of the administration of homologous or heterologous serum to mice before radiation. Partial protection was afforded which was comparable to that of animals given a lower radiation dosage (approximately 800 r to 550 r). The activity is present in fractions II and III of Cohn. It is interesting that perfusion of the shielded spleen of a radiated dog produced an active material while that of a normal animal failed to do so. The important contribution of this experiment is that protection was analyzed in terms of life time rather than 30-day survival. Unfortunately, experimental groups in some instances were small.

It is known that whole blood offers little benefit of survival to animals during the hemorrhagic diathesis of radiation, and that temporary allevia-

tion of the bleeding by platelet transfusion does not prevent mortality. In the bone marrow syndrome with which we are dealing at dosage levels to 1000 r, regeneration of marrow is the primary essential demand. Maintenance of life by control of infection, hemorrhage, and anemia, plus possible use of a regenerative factor, are the primary aims in the present treatment of the immediate lethal effects of the radiation syndrome.

Variation in Endocrine Response

Continued interest in the effect of radiation on the endocrine system is to be expected. The possible role of radiation injury as a nonspecific stress, the intermediate consequence of varied tissue injury appearing in a scattered fashion, the obvious relation of endocrine and immune factors, all lead to specific inquiry into alteration in the endocrine balances of the radiated animal. Lack of good methodology is a distinct handicap. Absence of continued observations into the interrelated endocrine changes which occur within the body during both degeneration and repair phases of radiation injury complicates interpretation of the pattern. Many observations are contradictory. Many deal with the simple addition of an endocrine supplement without regard to the specific need of the animal at that time. The fact that vital processes are seriously disturbed by such supplementation is shown by the observed increased sensitivity to radiation following extirpation of endocrine glands.

It is known that adrenalectomy (65), hypophysectomy (66), and medical, surgical, or radioactive thyroidectomy increase the sensitivity to radiation. Adrenal supplements when given to the intact animal lower his resistance. The favorable response which may be observed following restoration of hormonal balance toward normal is indicated in work showing that physiological doses of cortisone increase mean survival time in adrenalectomized but not in intact irradiated rats (67). Administration of adrenocorticotropic hormone (ACTH) does not benefit the whole body irradiated animal. Recent studies on growth or somatotropic hormone (68) not only show no benefit but indicate that the animal may be adversely affected by the injection procedure. Spellman and co-workers (69) noted that daily administration of small doses of growth hormone prevented the increased mortality observed in irradiated mice injected with 0.2 to 0.5 cc. saline daily. Mateyko & Edelmann (70), in studies on direct pituitary, whole body and head shielded radiation indicate the definite sensitivity of the anterior pituitary to direct as well as whole body irradiation. Measurements unfortunately extend to only 24 hr. postradiation. Gonadotropin was depressed. Thyrotropin was initially increased and later depressed in hypophyseal exposure. In whole body exposure significant increase of thyrotropic factor was present at 24 hr. This compares with the initial rise in I^{131} uptake observed by Rust in the dog and the burro. Corticotropin remained high in the hypophyseal irradiated rat but after whole body irradiation the initial elevation was followed by a depression. Lane *et al.* (71) report a suppression of gonadotropin principles through the seventh day in

rabbits exposed to 1100 r total body radiation. Rugh & Clugston (72), noting a variation in radiosensitivity of female CF_1 mice during major phases of the estrus cycle, suggest that pre-estrus may be the most radioresistant stage because of high estrogen production. Mirand *et al.* (73) repeated previous observations that diethylstilbestrol and estradiol benzoate given during the seven days postradiation enhance survival while androgen has no effect. Spellman *et al.* (74), while observing that testosterone propionate enhanced morbidity and mortality in irradiated mice, noted that long-acting testosterone cyclopentyl propionate was beneficial. They assume this benefit to be related to anabolic action.

Certain studies on the adrenal are contributory. Observations of decreased ascorbic acid content in the adrenal gland following high or low doses of x-rays were confirmed (75). Oster *et al.* (76) noted that tissue ascorbic acid was decreased only in the adrenal and attribute this action to pituitary stimulation. Brayer (77) showed that 600 r total body radiation to the rat significantly increased corticosterone level in the adrenal gland. Rosenfeld *et al.* (78), in exposures of the irradiated isolated calf adrenal to perfused substrates, note an inability of the gland to carry out specific oxidation and hydroxylation. These changes parallel decrease in corticosterone output by corticotropin-stimulated irradiated glands (79) in which reduction in hydrocortisone, corticosterone, and unidentified chromogen occurs. They conclude that, in spite of lack of dramatic morphological change, the adrenal cortex must be considered a radiosensitive tissue.

Possible indication of endocrine effect on target tissue is shown in the work of Smith & Lewis (80) who performed mast cell counts on skin, mesentery, and cheek pouch after adrenalectomy, hypophysectomy, and treatment with ACTH and cortisone. While the number of cells was not altered, ACTH in animals with intact adrenals and cortisone resulted in vacuolation and granular conglomerates similar to those observed after whole body irradiation. It does not seem unreasonable to infer that endocrine factors may be intimately related to, or modify, the regeneration factor of Jacobson and Cole.

Additional information concerning the endocrine balance and irradiation injury is given in the experiments of Upton & Furth (81) who note that cortisone given preradiation (350 r) increased the incidence of lymphoma in a high leukemia strain of mice; when given postradiation, it reduced the incidence. The induced atrophy of lymphoid tissues and thymus was transient.

Analysis of the available information definitely indicates the radiosensitivity of endocrine glands. In order of sensitivity it would appear that the adrenal is much more affected than are the others. Whether this effect is primary or is secondary to effects elsewhere in the body is uncertain but in all probability both types of action contribute. Additional experimentation is necessary on variations in hormonal levels during injury and repair from radiation exposure. The critical importance of the endocrine system of various species must be considered in extrapolation of information from

tion of the bleeding by platelet transfusion does not prevent mortality. In the bone marrow syndrome with which we are dealing at dosage levels to 1000 r, regeneration of marrow is the primary essential demand. Maintenance of life by control of infection, hemorrhage, and anemia, plus possible use of a regenerative factor, are the primary aims in the present treatment of the immediate lethal effects of the radiation syndrome.

Variation in Endocrine Response

Continued interest in the effect of radiation on the endocrine system is to be expected. The possible role of radiation injury as a nonspecific stress, the intermediate consequence of varied tissue injury appearing in a scattered fashion, the obvious relation of endocrine and immune factors, all lead to specific inquiry into alteration in the endocrine balances of the radiated animal. Lack of good methodology is a distinct handicap. Absence of continued observations into the interrelated endocrine changes which occur within the body during both degeneration and repair phases of radiation injury complicates interpretation of the pattern. Many observations are contradictory. Many deal with the simple addition of an endocrine supplement without regard to the specific need of the animal at that time. The fact that vital processes are seriously disturbed by such supplementation is shown by the observed increased sensitivity to radiation following extirpation of endocrine glands.

It is known that adrenalectomy (65), hypophysectomy (66), and medical, surgical, or radioactive thyroidectomy increase the sensitivity to radiation. Adrenal supplements when given to the intact animal lower his resistance. The favorable response which may be observed following restoration of hormonal balance toward normal is indicated in work showing that physiological doses of cortisone increase mean survival time in adrenalectomized but not in intact irradiated rats (67). Administration of adrenocorticotropic hormone (ACTH) does not benefit the whole body irradiated animal. Recent studies on growth or somatotropic hormone (68) not only show no benefit but indicate that the animal may be adversely affected by the injection procedure. Spellman and co-workers (69) noted that daily administration of small doses of growth hormone prevented the increased mortality observed in irradiated mice injected with 0.2 to 0.5 cc. saline daily. Mateyko & Edelmann (70), in studies on direct pituitary, whole body and head shielded radiation indicate the definite sensitivity of the anterior pituitary to direct as well as whole body irradiation. Measurements unfortunately extend to only 24 hr. postradiation. Gonadotropin was depressed. Thyrotropin was initially increased and later depressed in hypophyseal exposure. In whole body exposure significant increase of thyrotropic factor was present at 24 hr. This compares with the initial rise in I^{131} uptake observed by Rust in the dog and the burro. Corticotropin remained high in the hypophyseal irradiated rat but after whole body irradiation the initial elevation was followed by a depression. Lane *et al.* (71) report a suppression of gonadotropin principles through the seventh day in

rabbits exposed to 1100 r total body radiation. Rugh & Clugston (72), noting a variation in radiosensitivity of female CF_1 mice during major phases of the estrus cycle, suggest that pre-estrus may be the most radioresistant stage because of high estrogen production. Mirand *et al.* (73) repeated previous observations that diethylstilbestrol and estradiol benzoate given during the seven days postradiation enhance survival while androgen has no effect. Spellman *et al.* (74), while observing that testosterone propionate enhanced morbidity and mortality in irradiated mice, noted that long-acting testosterone cyclopentyl propionate was beneficial. They assume this benefit to be related to anabolic action.

Certain studies on the adrenal are contributory. Observations of decreased ascorbic acid content in the adrenal gland following high or low doses of x-rays were confirmed (75). Oster *et al.* (76) noted that tissue ascorbic acid was decreased only in the adrenal and attribute this action to pituitary stimulation. Brayer (77) showed that 600 r total body radiation to the rat significantly increased corticosterone level in the adrenal gland. Rosenfeld *et al.* (78), in exposures of the irradiated isolated calf adrenal to perfused substrates, note an inability of the gland to carry out specific oxidation and hydroxylation. These changes parallel decrease in corticosterone output by corticotropin-stimulated irradiated glands (79) in which reduction in hydrocortisone, corticosterone, and unidentified chromogen occurs. They conclude that, in spite of lack of dramatic morphological change, the adrenal cortex must be considered a radiosensitive tissue.

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animal to man. One should warn against indiscriminate use of adrenal supplements in therapy of radiation hazard, as suggested by Taber (82), unless positive evidence of a specific deficiency is determined by clinical and laboratory observations.

Late or Irreversible Effects of Radiation Injury

Survival from the acute effect of a single large dose of ionizing radiation does not mean that the individual recovers completely from the physical changes or the biochemical alterations following such change. It appears that certain tissues such as the hematopoietic and gastrointestinal system possess extraordinary ability of regeneration. This regeneration in most species seems to be a maximal response in a tissue which, as a normal function, continually elaborates new cells. While abnormality exists in the healing process in these tissues during early phases, ultimate hypertrophy and return to normality leaves few physiological or morphological scars behind. On the other hand, tissues whose regenerative powers are more limited may not demonstrate profound degrees of morphological change but react to the stress of ionization with minute but abnormal difference in function which cannot be analyzed by present crude methods. Should whole body irradiation damage many tissues of the body in a minimal fashion, one might expect that a significant portion of the animal's life would pass before the accumulated damage would affect the individual. It has long been appreciated that whole body radiation produces lasting effects in the form of aging, induction of cancer, sterility, cataract formation, and genetic changes. Effects observed are related to dosage, whether acute, subacute, or chronic, type of radiation, and species, as well as unknown physiological factors. In general, acute high dosage produces maximal effect as regards aging. Repeated large but sublethal dosage results in similar effects, but the amount of radiation required is substantially greater as the dosage decreases and time interval between subsequent radiations increases. Results vary with the species and unfortunately the aging effect in most laboratory animals has been so little studied that changes other than comparative death times are difficult to interpret. Most studies have been carried out on mice and rats because of difficulties in carrying out life span experiments with larger animals having longer lives.

Interest in effects of radiation on longevity is stimulated by the increasing use of radiation and radioactivity in this atomic age. Attempts are being made to assay the injury and recovery phases and to quantitate the biological effect of a given exposure or exposures in terms of residual or irreversible injury. In a series of papers Blair (83 to 86) has formulated a hypothesis that injury develops in proportion to the dose rate and is repaired spontaneously at a rate proportional to its magnitude except for an irreparable amount which in turn is proportional to the total accumulated dose. This hypothesis has been workable with mice chronically irradiated with both x-rays and neutrons, gamma irradiation of guinea pigs, and x-radiation of

rat and dog. A calculated value of approximately 7 per cent was made for reduction in life span per 1000 r accumulated dose of x- or gamma radiation providing recovery has been permitted to take place as far as it would. This is true only for divided doses; large single doses, at least in excess of 200 r, shorten life about 35 per cent per 1000 r. The irreversible effects of particulate radiations are greater than those of x-rays. Suggestion is made that the sum of processes which are measured by reduction of life span of a species is perhaps more representative than analysis of any specific function. Protective or therapeutic agents to provide maximal benefit must not only reduce in time the phase of acute reparable injury, but also enhance regeneration. Sacher (87) constructed a mathematical comparative analysis from available existing data and information on the basis that (*a*) many or all aspects of physiologic function are affected by radiation, (*b*) the responses of physiologic systems are linear, (*c*) a lethal process arises which is a weighted sum of injuries to the constituent systems, (*d*) death occurs when this process interacts with a lethal amount of injury, and (*e*) when aging is a significant factor, the effects of the aging process and the radiation process combine additively. Present information falls far short of ratifying these criteria, but as added information becomes available it would permit not only the better understanding of the process but would permit extrapolation of information from species to species. If, on the other hand, a summation effect such as aging can be used, much useful information on chronic effects can be gained from carefully planned and executed experiments. In regard to life time study Lorenz *et al.* (88) noted that chronic gamma radiation of LAF_1 mice at 0.11 r/day from one month of age throughout life showed no life span reduction and significantly enhanced survival in the males. Incidence of tumors in irradiated animals was increased. At this dosage level it might be considered that residual damage was not sufficient to be effective in the aging process of these mice.

With certain tissues, effects of radiation are apparently short-lived and the demonstration of residual defects is difficult. Repetitious exposure of male rats to 75 r at seven-day intervals by Baum *et al.* (89) showed that the maximum hematologic changes were independent of the number of exposures and reflected the effects of the last exposure. Michaelson (90), in experiments on hematologic recovery in the dog, noted that repeated radiation exposures of 300 r or more at five-week intervals essentially duplicated each other, and no change in response of the individual animal was observed. On the other hand, other tissues with different reaction times may behave dissimilarly. Fogg & Cowing (91) noted in radiation of testes of partially shielded animals with sublethal dosages of 138 and 300 r that the effect on spermatogonia and prespermatogonia was best observed between five and eight days after exposure. Repeated doses of irradiation after an initial 138 r were given at one, two, four, or eight days and produced similar changes at the same interval. Recovery of spermatogonia was delayed after the second dose. Reactivity at the one-, two-, four-, or eight-day period does

not confirm a reduced reactivity after initial radiation. Kohn & Kallman (92) gave whole body radiation to CAF_1 mice and used weight of the testes as the criterion of injury. Dosage range was 80 to 240 r in two to five fractions administered in one to four days time. Degree of injury was proportional to total dose and not affected by fractionation. Data support the hypothesis that one radiological event inactivates one biological unit, possibly a spermatogonium. Differences in the two experiments are possibly related to the presence of effects from nonradiated tissue in the shielded animals. Casarett (93) gives preliminary reports on dogs given whole body radiation at dosage levels of 0.3 r/week, 0.6 r/week, and 3.0 r/week starting at three months of age. Changes were produced in the 3.0 r/week animals at a total accumulated dose of 264 r in two animals and of 219 r in another. These changes include drop in absolute sperm count to 10 per cent of preirradiation values with no change in per cent of live sperm. The per cent of motile sperm decreased, owing to abnormal forms. These three animals, tested by mating, produced no pups at accumulated doses above 150 r. Mating at lower levels gave litters of considerable size. One may conclude that impairment in function can occur with an accumulated dose in a specific test system even though evidence of damage does not exist in other cells and tissues.

Other experiments on the persistence of irreparable injury in animals surviving large radiation dosages by means of protective measures are given by Dowdy & Bennett (94). Rats surviving doses of 500 r and animals irradiated in the anoxic state showed shortening of life span proportional to dose. Death was variously contributed to by susceptibility to infection, malignant changes, and anemia. Other types of abnormality included cataracts, alteration of the media of arterioles, nephrosclerosis, hypertension, splenomegaly, reticulocytosis, thrombocytopenia, and minor changes.

It is distinctly unfortunate that most investigators using protective and therapeutic factors have not developed an interest in residual effects following recovery from profound hematological or gastrointestinal injuries with their complications of infection, hemorrhage, and anemia. Individuals working with protective compounds have adopted the 30-day mortality figure as a standard end point. In mice with short life span, observations over the subsequent 120 days might reveal many differences in the physiological or pathological picture which could easily direct inquiry into possible basic mechanisms. Stroud, Brues & Summers (64) consider this possibility in their studies on the nature of the radiation protection with prophylactic administration of a blood protein fraction and correlate it with survival curves on mice radiated at different levels. One notes that the protection of cysteine reduces dosage from 800 to 650 r and the blood factor to 575 r equivalent. Cysteine plus the factor reduces dosage to 475 r and doubling amounts to even greater extent. It is important to consider the possibility that, in these experiments, two protective mechanisms are operative. A similar situation was encountered in this laboratory (95), in which it was noted that significant protection against 450 r exposure in dogs can be

achieved by use of chlortetracycline with no effect at 550 r. Addition of an ascorbic acid, B_{12}, liver fraction (Perihemin) produced the same improvement with 550 r as was observed at the lower level with the antibiotic alone. This would suggest that radiation effects are general and that proper treatment at best is directed toward correction of a series of individual defects. It is very important to discover what these defects are; study of recovering animals from various levels of acute or subacute radiation dosage may be the only solution to the problem.

Other experiments bearing on the chronic effects of acute radiation exposures are few. Upton, Furth & Christenberry (96) in a study of the comparative effects of thermal neutrons and x-ray irradiation find essential similarity between them except for the higher effectiveness of neutrons in cataract formation. Furth *et al.* (97), in a 30-month observation on a large group of mice following nuclear detonation, record mortality, aging, tumor induction atrophy of iris, cataract formation, and depression of reproduction. In analysis they consider that certain neoplasms in ovary, pituitary, and breast may not be induced by direct change but follow an imbalance of normal regulatory mechanisms. Ovarian tumors appear to be related to pituitary-ovary imbalance, hypophyseal to adrenal-pituitary, and mammary to general change. Upton & Furth (98) noted that the spontaneous incidence of pituitary tumors in LAF_1 mice was enhanced by single whole body exposure to ionizing radiation, with the tumor formation being hastened in proportion to the dose. Analysis of all data suggests that the higher incidence of tumors is related to the aging process rather than to a specific carcinogenetic mechanism.

Dent, Gadsden & Furth (99) studied pituitary tumor formation following thyroid depression by surgical extirpation, or surgical extirpation and injection of I^{131} in varying doses, with grafting of dependent thyrotropic pituitary tumor, to C57 BL mice. They note that surgical thyroidectomy as well as I^{131} thyroidectomy results in an increased number of pituitary tumors, that surgical thyroidectomy is as effective as I^{131} thyroidectomy in conditioning hosts for dependent pituitary tumors, and that adenomatoid hyperplasia of thyroid in thyroid remnants results from both procedures. They conclude that radiation is not an essential factor in tumor formation under these conditions.

Upton & Furth (100), in a study of pituitary tumors produced by a single exposure to ionizing irradiation in mice, noted greatest incidence in animals exposed to doses below the LD_{50}. Neutrons were more effective than gamma rays. Higher incidence among females and the long period of latency may indicate the importance of aging and related endocrine changes in induction of these tumors. Koletsky & Gustafson (101) exposed a series of rats to 660 r and noted an increased incidence of tumors with duration of life span. Of 69 tumor-bearing irradiated animals, 43 had one or more malignant neoplasms. Of 36 controls 22 showed tumors, 7.3 per cent of which were malignant. The authors postulate an indirect or systemic mechanism induced by the radiation.

Furth & Upton (102) review the existing information on leukemogenesis by ionizing irradiation and conclude that all types of ionizing radiations are leukemogenic, the rate varying with the total dose, dose rate, and fractionation interval. Single dose exposure below 400 rep is negligible in results so far observed. Both myeloid and lymphoid types were noted. Reduction in incidence of lymphomas occurred on administration of cortisone if certain time relations to irradiation were observed. Deringer, *et al.* (103) exposed newborn HR mice to 400 r whole body radiation and noted not only life shortening but increased incidence of ovarian tumors. The same dose failed to increase incidence of papillomas of skin but did shorten time of appearance of these lesions. From the presented data, rough calculation would indicate that the appearance of papillomas is directly related to the aging process in these animals. Deringer *et al.* (104), using hybrid mice, compared exposure of ovaries alone with whole body radiation at ranges of 12.5 to 400 r and 500 r to ovaries only. Females exposed up to 50 r to whole body, and to 200 r to ovaries only, continued to produce litters. Above 100 r litter size was reduced. Above 50 r whole body and 200 r to ovaries only a single litter was produced. Ovarian tumors occurred in all animals with doses of 300 r and above to the ovaries, and with 100 r and above to the whole body. No tumors occurred in the controls or in ovary-shielded animals. Life shortening effects do not appear to be high in these groups so that the greater effect of the whole body irradiation must be related to alterations in the balance between the ovaries and the remainder of the body. This contribution of other factors toward induction of tumors is indicated in the latest experiments of Kaplan *et al.* (105) who previously observed that lymphoid tumor development in irradiated strain C57 BL mice could be inhibited by spleen or thigh shielding during irradiation or injection of homologous bone marrow postradiation. Further experiments presented indicate that bone marrow injection maximally inhibits tumor formation if given within $1\frac{1}{2}$ hr. of the radiation. This inhibition decreases in a linear relation up to 16 days at which time it is lost.

Cloudman *et al.* (106) present experiments indicating the additivity of chemical and radioactive carcinogens. Salerno & Freidell (107) comment on the synergism of action of two radioactive materials, Au^{198} and P^{32}. Koletsky & Christie (108) note induction of neoplasms in rats by doses of P^{32} greater than one microcurie/gram body weight.

Added observations continue to appear concerning late effects of the atomic explosion on the Japanese. In addition to the increased incidence of leukemia and cataracts previously reported, Yamazaki *et al.* (109) report on the outcome of pregnancy in women exposed to the atomic explosion in Nagasaki. A study of 30 exposed mothers showed seven fetal deaths, six neonatal, and six infants deaths, and in 16 surviving children, four instances of mental retardation. This overall morbidity and mortality of 60 per cent contrasts with a 10 per cent incidence in mothers in the same area with less exposure, and 6 per cent in controls with no exposure. Major abnormalities observed were decrease in height and in head circumference (microcephaly).

Miller (110), in analysis of data from Hiroshima, noted that in 33 microcephalic children who were exposed *in utero* to the atomic bomb, development of the abnormality was directly related to distance from the hypocenter and gestational age. Mental retardation was observed in 15 of the 33 patients. An increase in leukemia in exposed youths 19 years or less in age was noted. Studies now in progress appear to indicate that aging processes in exposed individuals may be accelerated but it is too early for accurate assay of this problem. No other abnormalities of embryonic origin have been demonstrated.

A major development is the recognition by health authorities of the potential hazard of chronic exposures. Many have adopted health codes or regulations in anticipation of a future problem. Others have the question under serious consideration. The publication of Handbook 59 (111) on *Permissible Dose from External Sources of Ionizing Radiation* of the National Committee for Radiation Protection has been of tremendous value to interested groups. This reflects the general emphasis in the field of radiation research which is extending its interests into the peacetime use of radiation and to the problems related to chronic radiation which accompany such conversion.

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DISEASES OF THE KIDNEY[1]

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ASPIRATION BIOPSY OF THE KIDNEY TISSUE

Some years ago Pérez (1) and Iversen & Brun (2) independently published methods of aspiration biopsy of the kidney. With this technique it became possible to obtain sufficient kidney tissue for histological studies in man without any serious risk.

Results obtained by this method have been published in a series of papers from Kommunehospitalet in Copenhagen (3 to 14) in which special importance was attached to the comparison between the histological and functional changes as revealed by differential kidney function tests.

A number of investigators in other countries have taken up the method (15 to 25), and the literature on kidney biopsy is rapidly growing. Advances in technique have been contributed by Payet, Pene, Camain, Gouaze & Calvez (25) and by Kark & Muehrcke (17), especially with regard to the immobilization of the kidney and its accurate localization.[2]

The value of kidney biopsy is theoretical as well as practical. As it is possible to study mild cases of kidney disease and very early stages of more pronounced cases, the procedure is an important tool with which to obtain new information on the natural history of kidney disorders. From a therapeutic point of view, too, kidney biopsy is of considerable importance, especially in acute renal failure.

Technique

The present technique, modified from that described by Iversen & Brun (2), includes the important improvements of Kark & Muehrcke (17); their exploring needle is used, and the patient lies prone with a sandbag under the abdomen. Our technique involves an aspiration biopsy, with which one has a greater possibility of obtaining a longer bit of tissue, as illustrated in Figure 1.

Risks in Kidney Biopsy

We have not observed fatal complications with the kidney biopsy method. Transitory, microscopic hematuria is generally observed when the kidney has been punctured, but macroscopic hematuria is seen. Postmortem examinations of the site of the kidney puncture were made in a small num-

[1] The survey of literature pertaining to this review was completed in April, 1955.

[2] After the completion of this manuscript, three important papers by Kark, Muehrcke and collaborators appeared (35, 36, 37). It is not possible to include their papers in the present review, but readers should refer to them for excellent description of technique and additional evidence on the clinical value of kidney biopsy. Others have also published further material (38, 39, 40).

ber of cases. In a few of these a small hematoma was found in the renal capsule or in the pelvis, but in most cases the site of the puncture could not be demonstrated. Among 50 biopsy experiments Parrish & Howe (23) have had one complication: kidney biopsy performed with a Turkel biopsy instrument evoked a large retroperitoneal hematoma; it was located, drained and packed, and the patient made an uneventful recovery.

Contraindications

It is universally accepted that hemorrhagic diathesis is a contraindication. The same applies to hydronephrosis and pyonephrosis, renal aplasia and perirenal abscess. On the other hand, kidney tumors and cysts can hardly be considered contraindications, as suggested by Kark & Muehrcke (17). Zelman (26) has postulated that needle biopsy is contraindicated in uremia on account of hemorrhagic diathesis; in our opinion, hemorrhagic diathesis does not accompany uremia so frequently that the latter can be accepted as a general contraindication.

Renal Histology in Various Kidney Disorders

Acute anuria.—Space does not permit a thorough review of the histological changes which have been described by a large number of investigators [Bywaters & Beall (27); Dunn, Gillespie & Niven (28); Bywaters & Dible (29); Lucké (30); Mallory (31); McManus (32); Bell (33); Iversen & Brun (2); Zollinger (34)]. A summary of the most important histological changes observed in biopsy material (7, 8, 10) is as follows: (*a*) low, flattened epithelium of the proximal convoluted tubules and occasional dilatation of these tubular portions, (*b*) dilatation of the distal convoluted tubules and ascending limbs of Henle's loops with attending flattening of the epithelium, (*c*) localized hydropic changes in the protoplasm of the epithelial cells in the proximal convoluted tubules, (*d*) degenerative and regenerative processes, often side by side, in the tubular epithelium, (*e*) interstitial changes consisting of focal or diffuse edema with or without cellular infiltration of varying intensity and character, (*f*) occurrence of hemoglobin-pigmented casts in the distal convoluted tubules, Henle's loops, and collecting tubules.

The histological changes found in biopsies seem to differ from the traditional descriptions at two points: first, the interstitial changes are very dominant, and secondly, frank necroses have not been observed. Even if allowance is made for the limited amount of tissue studied in each case it is noteworthy that no necroses are observed although the cases were severe enough to present a long-standing anuria. It is possible that necroses are more common in the very severe cases observed during World War II than in civilian cases.

Glomerulonephritis.—(*a*) Acute glomerulonephritis.—Twelve patients whose diagnosis had been established clinically as acute glomerulonephritis have been studied by kidney biopsy (9). Clinically and patho-anatomically these 12 cases could be divided into two distinctly different groups:

Group A comprised five very severe cases. They all had severely reduced kidney function, uremia, and oligo-anuria. They all died. Glomeruli in all five cases were severely affected with extensive fibrinoid necroses, pronounced endothelial and epithelial proliferation, synechiae and crescents; interstitially there was a varying degree of edema and inflammatory infiltration. On the basis of the biopsy findings it could be said at once that the changes were undoubtedly irreversible, and that hemodialysis therefore must be considered futile in all five cases.

Group B consisted of seven mild to moderate cases, in whom kidney function was normal or only slightly reduced when biopsy was performed. None of these patients had uremia or oligo-anuria. The kidney biposies showed only slight changes, viz. slight to moderate hyalinizations in the glomeruli and varying degrees of endothelial and epithelial proliferation, but neither fibrinoid necroses nor crescents, and interstitially very slight changes, or none.

It is impossible to decide on the basis of this small series whether these two different groups represent simply a different degree of gravity of the same acute kidney disease, or whether they exemplify two fundamentally different forms of glomerulonephritis.

There was complete accord between the clinical and laboratory diagnosis and the biopsy findings with regard to the gravity of these 12 cases, whereas there was less conformity between clinical and biopsy findings with respect to the assessment of the duration. This discrepancy was presumably due to the fact that the histological changes in the glomeruli were considered older than they actually were.

Crescents and adhesions were demonstrated, at the earliest, on the twelfth to sixteenth day of the disease and pronounced collagenic-hyaline changes or complete hyalinization of the glomeruli at least as early as the fifteenth day of the disease, in some cases in conjunction with typical, acute changes. Crescents and adhesions as well as pronounced collagenic-hyaline glomerular changes thus undoubtedly belong to the histo-pathological picture of acute glomerulonephritis. The apparent discrepancy between the clinical and the histological assessments of the duration of the cases is presumably the result of inadequate criteria caused by the lack of knowledge so far of the histological changes in the early phases of acute glomerulonephritis.

One case seems to show that severe, acute glomerulonephritis may lead to almost completely destroyed, hyalinized glomeruli in the course of 35 days.

(*b*) Acute exacerbation in chronic glomerulonephritis.—This clinical diagnosis was confirmed by kidney biopsy in one case, whereas another case was revealed as one of severe amyloidosis of the kidneys (9).

(*c*) Chronic glomerulonephritis (without edema).—Four cases have been published in which this diagnosis has been clinically established (9). The biopsies confirmed the diagnosis but were otherwise noncontributory.

The nephrotic syndrome.—The nephrotic syndrome is one of the domains

in the pathology of the kidneys in which the biopsy method may be especially contributory to an etiological diagnosis. In eight cases with this syndrome kidney biopsies were performed (3); the biopsies showed that no less than four patients had amyloidosis of the kidneys; the other four had chronic glomerulonephritis. Two had hardly any glomerular changes, and were perhaps cases of so-called "genuine lipid nephrosis," if this disease exists. Kidney biopsy was of diagnostic importance especially in the cases of amyloidosis of the kidneys wherein the underlying disorder did not manifest itself distinctly in the clinical picture.

In serial kidney biopsy studies it has been found (21) that the earliest morphological lesion in the nephrotic syndrome with subacute glomerulonephritis was moderate to severe fatty degeneration of the tubular cells with normal glomeruli; thickenings of the basement membranes, increased content of cells, and crescents in the glomeruli were not observed until later.

As it has been ascertained in other investigations that the proteinuria in the nephrotic syndrome is due to altered permeability of the glomerular membrane, it can be concluded from the investigations mentioned above (21) that very pronounced functional changes may occur in the glomeruli simultaneously with few histological changes. Similarly, the severest degrees of proteinuria tended to occur in patients with comparatively few glomerular changes, whereas considerable histological changes of the glomeruli as a rule occurred in patients with comparatively little proteinuria (3, 15).

Diabetic nephropathy.—In 12 patients suffering from diabetes mellitus the results of kidney biopsy were compared with the clinical and laboratory findings and with the differential kidney function tests (6).

In six cases biopsy revealed purely diffuse, glomerular changes, in four cases nodular-diffuse changes, in one case completely hyalinized glomeruli with remnants of glomeruli, and in one case, biopsy showed normal kidney tissue in a patient in whom the later course showed that the nephrotic symptoms really had been caused by heart failure.

In four cases, without clinical signs of diabetic kidney disease, the biopsy revealed the presence of glomerular changes (in three cases diffuse, in one nodular-diffuse).

This investigation apparently supports the theory that diabetic nephropathy begins as a diffuse hyalinization of the basement membranes of the glomerular coils, and that the nodular changes may be considered a further development of the diffuse ones (33).

Chronic pyelonephritis.—Thirteen patients with chronic infection of the urinary tract have been studied by kidney biopsy (18). In four patients normal kidney tissue (and normal kidney function) was found, in four patients, evidence of chronic pyelonephritis (and reduced kidney function). Among the remaining five patients, healed pyelonephritis was found in one, cystic kidney in one, hydronephrosis in one, and nephrosclerosis in one. These investigations seem to suggest a good correlation between morphology and function, even in such a focal kidney disorder as pyelonephritis. However,

the authors do not discuss the question of the importance of kidney biopsy in the differential diagnosis between pyelonephritis and other types of chronic nephropathy. The same authors made cultures from the biopsy material, but findings were positive in two cases only. Kidney biopsy did not give rise to exacerbations of the infectious renal disease.

Other disorders of the kidney.—(*a*) Multiple myeloma.—Kidney biopsy was performed on five patients with myelomatosis and nephropathy; they showed diffuse histological changes, but none which could be considered specific of myelomatosis (16).

(*b*) Nephrocalcinosis.—The results of kidney biopsy in two cases of renal calcinosis have been reported (5); one was a case of hyperparathyroidism, the other was one of calciferol (vitamin D_2) intoxication.

(*c*) Sarcoidosis.—Kidney biopsy was performed on two patients with generalized sarcoidosis and reduced kidney function (20); specific granulation tissue and calcium deposits were found.

(*d*) Disseminated lupus erythematosus.—Kidney biopsy has been performed in a single case of disseminated lupus erythematosus (19). The characteristic "wire-loop" lesions were observed in the glomeruli, while biopsy of the skin and search for the L. E. cell phenomenon gave negative results.

(*e*) Bilateral cortical necrosis.—The diagnosis of acute bilateral necrosis has been established with kidney biopsy in a woman with complete anuria, (8, 10). The uremia persisted for a long time, and peritoneal dialysis was therefore performed with eventual recovery.

Kidney Biopsy as a Diagnostic Method

The practical value of kidney biopsy cannot at present be accurately assessed, as the method is too new. Experience so far, however, seems to indicate that it can contribute to the diagnosis and the prognosis of kidney diseases.

The diagnostic value of kidney biopsy has been proved by the results obtained in patients with acute anuria, nephrotic syndrome, diabetic nephropathy, and acute glomerulonephritis. As for the group with anuria, it is possible by means of kidney biopsies to divide them into subgroups, dependent on the etiology of the acute renal disorder (e.g., shock, hemolysis, bilateral cortical necrosis, etc.). In this connection it may be mentioned that biopsy also enables us to distinguish with certainty anuric cases of glomerulonephritis (acute or chronic) and amyloidosis of the kidney from other forms of anuria. With regard to the nephrotic syndrome, it can be divided into renal amyloidosis, subacute and chronic glomerulonephritis. Differential diagnosis of diseases such as these, which have the same symptomatology but widely different etiology and clinical course, seems to be possible only with kidney biopsy. Kidney biopsies in 12 patients with diabetes mellitus have demonstrated the value of this diagnostic method in diabetic nephropathy. In some cases, in which biopsy merely confirmed the clinical diagnosis, it nevertheless afforded information about the nature of the glomerular

changes. This may possibly be of prognostic significance. In others, particularly in those without proteinuria, biopsy gave the clue to incipient renal disease, which could not yet be diagnosed clinically. In cases of clinically diagnosed acute glomerulonephritis, too, the biopsy method may prove of value in diagnosis and prognosis.

Value of the Kidney Biopsy Method in the Choice of Treatment

Finally, it may be pointed out that the kidney biopsy method may support us in choosing the method of treatment. If a kidney biopsy in a case of acute anuria reveals a pronounced hyalinization of the glomeruli, indicative of chronic kidney disease, or acute, necrotizing, irreversible glomerular changes, suggesting the presence of severe acute glomerulonephritis, we should, of course, be reluctant to institute hemodialysis. As another example all of our patients with nephrotic syndrome were treated with corticotropin (ACTH) (4); apparently the cases showing the slightest histological changes in the kidney biopsy were those that responded best to the therapy.

In addition to what has been mentioned, it may be anticipated that in future the kidney biopsy method will be valuable in other fields. Serial examinations in the same patient may, for instance, contribute to an understanding of the course and prognosis of various renal diseases; furthermore the method can be used in enzyme studies and in measurements of tissue metabolism.

In our opinion, biopsy will permit a fruitful study of the relation between renal anatomy and function. The refinement of renal function tests in general and the quantitative aspects of these functions in particular, give every reason to expect even better results from biopsy of the kidney than have been obtained with liver biopsy.

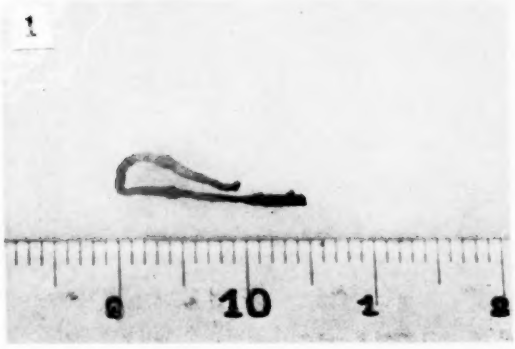
ACUTE RENAL FAILURE (ISCHEMIC ANURIA)

Acute Renal Failure is a very broad term which may cover almost any severe, acute disorder of the kidneys. The term by definition includes a great diversity of conditions such as: acute glomerulonephritis, obstruction of the urinary tract, prerenal azotemia, renal damage due to nephrotoxic poisons, and renal failure following shock. In current usage the term refers particularly—if not exclusively—to the last named condition.

Terminology

Various investigators have coined names for this disturbance: Traumatic Anuria (1), Lower Nephron Nephrosis (2), Tubular Nephritis (3), Hemoglobinuric Nephrosis (4), Shock Kidney (5), Tubular Necrosis (6), and Ischemuric Episode (7) are some of the more well-known names used in recent literature.

It does not seem feasible to choose a patho-anatomical name for a disorder in which the severity of the histological changes by no means parallels the functional disturbances and can be negligible in spite of pronounced



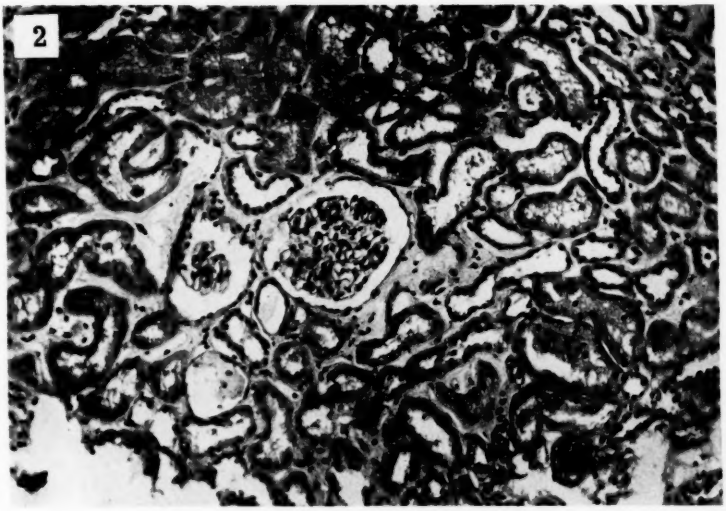
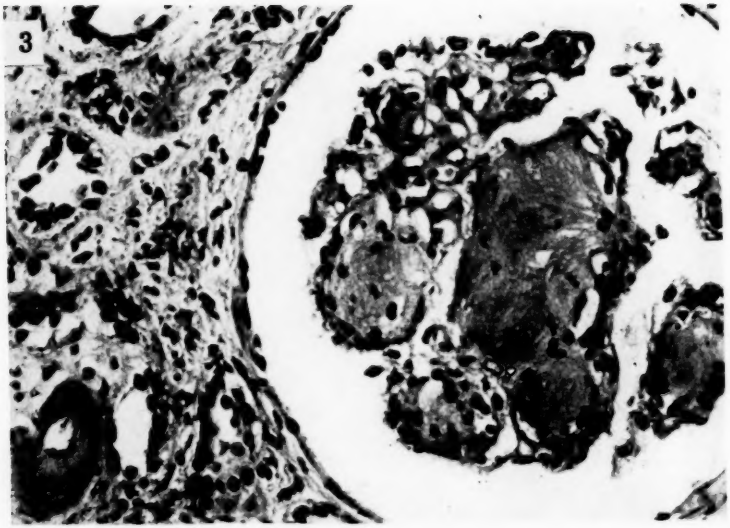


FIG. 1. (Above) Size of an aspiration biopsy of the kidney (cm.).

FIG. 2. (Below) Kidney biopsy in sulfonamide reaction with acute renal failure. Practically normal kidney tissue (8) (×140).



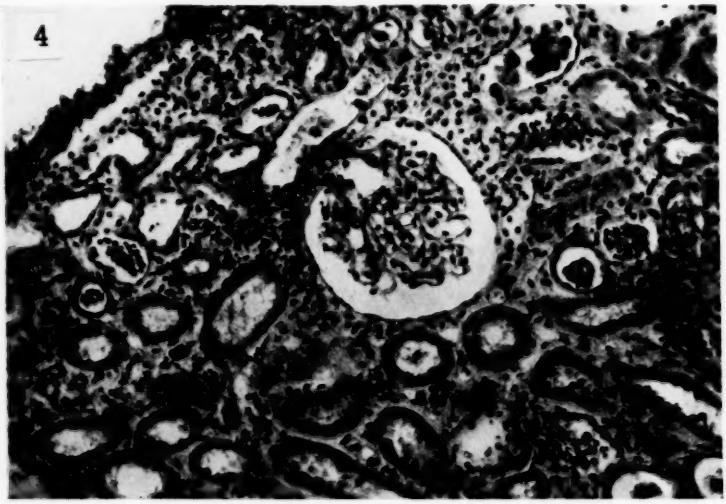


FIG. 3. (Above). Kidney biopsy in diabetic nephropathy (Kimmelstiel-Wilson) (×300).

FIG. 4. (Below). Biopsy specimen of kidney with such severe interstitial changes that the tubules lie separated. Marked cellular infiltration by lymphocytes, histiocytes, few plasma cells, and rare leucocytes. The proximal tubules have a low epithelium. In the distal convoluted tubules hemoglobin-pigmented casts are seen, containing leucocytes, lymphocytes, and nuclear fragments (8) (×140).

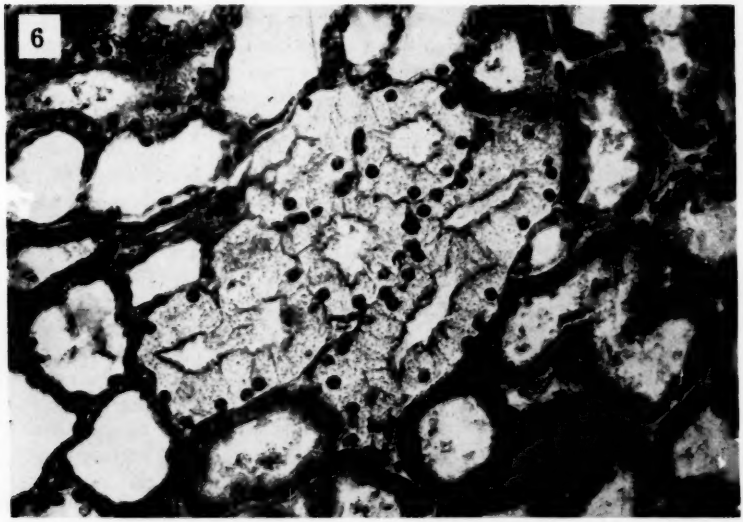


FIG. 5. Kidney biopsy in ischemic anuria. Hydropic changes in proximal tubules (just to right of normal glomerulus). Flattened epithelium in the distal tubules, one of which (left of glomerulus) contains a heme cast. Interstitial edema and cellular infiltration (8) (×300).

FIG. 6. Early fixed postmortem specimen in ischemic anuria. Flattened epithelium in distal, hydropically changed epithelium in proximal tubules (8) (×300).

abolition of renal function. A prolonged renal ischemia, in most cases provoked by shock, is now generally accepted as a main pathogenetic factor. Consequently the term Ischemic Anuria is suggested as a name for this clinical syndrome (8).

Incidence

The importance of ischemic anuria in military and civilian medicine is steadily increasing as advances in surgery, medicine, resuscitation, etc. make possible the survival of still more desperately ill or severely injured patients.

In World War II renal lesions were found in 18.6 per cent of 427 unselected battle casualties who died in army hospitals (4), and 40 per cent of one group of severely wounded patients developed acute posttraumatic renal insufficiency with a case fatality of 90 per cent among the severely oliguric (9). In the Korean war the problem was of equally major importance. The unusually prompt evacuation by helicopter made possible the early treatment of casualties with massive injuries. Of this group 35 per cent developed azotemia and clinically evident uremia. Among 165 battle casualties autopsied, histological evidence of renal damage occurred in 39 per cent and clinical uremia was considered severe enough to account for death in 14 per cent of the cases (10).

The types of renal insufficiency seen in war are not qualitatively different from those generally seen in civilian medicine, but the rate of development of clinical uremia and potassium intoxication is greatly enhanced and the case fatality rate is excessively high.

Pathogenesis

In Korea during 1952, 51 patients who developed "posttraumatic renal insufficiency" and were admitted to the Renal Insufficiency Center were thoroughly studied with respect to the pathogenetic factors and clinical manifestations, and a comparison made between these patients and a control group of 41 severely wounded who did not develop uremia (10).

From this evaluation it appears that inadequate or delayed volume therapy may have been a contributing etiological factor. The renal failure group received an average of 5.9 liters (range, 0.5 to 15.5) of blood, plasma etc., while the control group averaged 12 liters during the immediate postwound period. No great difference could be found between the two groups with respect to evacuation time (4.6 hr. against 3.5 hr.) and duration of hypotension (7.3 hr. against 6 hr.). While hemolysis could be shown to play no important role, the severity of the wound and its localization (the trunk, especially when including the kidney) seemed to be of importance. It was furthermore found that acute renal failure was impending when an excessively large volume of blood was required to correct hypotension.

The experiences from Korea seem to bear out the theory that shock is a main etiological factor in this type of renal failure. Extensive studies on the effect of shock on renal function in man and experimental animals (11, 12,

13) have shown that in shock due to hemorrhage or trauma the renal blood flow is severely reduced or practically abolished. As Van Slyke states "It is as though the kidney decreases its own circulation in order to maintain that of the heart and brain. Since the normal renal blood flow is about 20 per cent of the cardiac output during rest, there is an obvious advantage to the organism in a mechanism for commandeering blood from the kidney, in time of vital need" (14).

Further support for the theory that renal ischemia during shock is the cause of injury is found in functional (15 to 19) and histological (4, 15, 20, 21) studies on kidneys after clamping of the renal artery. Of special importance are the microdissections of individual nephrons by Oliver, MacDowell & Tracy who state that it is possible by transitory clamping to produce histological changes similar to the lesions developed after experimental shock and resembling the lesions found in human cases after ischemic anuria (7).

Mechanism of Anuria

The mechanism of the complete or nearly complete abolition of urine flow in ischemic anuria is by no means clearly understood. The following hypotheses have been advanced:

Obstruction of the renal tubules.—In spite of "the obvious conclusion that fluid cannot flow readily through plugged conduits" as Oliver (22) puts it, most investigators regard the formation of casts as a consequence of oliguria rather than a cause. This view is supported by lack of correlation between the degree of functional renal damage and the number of casts (4, 23, 24).

However, even if little or no importance can be attached to the casts for initiation of anuria, their presence may very well be conceived to present a difficulty when urine production starts again.

Nonselective subtotal reabsorption of glomerular filtrate.—If nonselective back diffusion were the main factor in ischemic anuria, clearance ratios between substances of different molecular size should be expected to show a characteristic deviation from normal values. This does not seem to be the case, either during oliguria or in the diuretic phase (8). As a sole explanation of anuria in ischemic anuria this theory is hardly acceptable.

Interrupted continuity of tubules with leakage of filtrate into interstitial tissue.—The anatomical basis for this mechanism may in some measure be present in ischemic anuria, where localized necrosis of the tubular wall with dissolution of the continuity (tubulorhexis) has been observed (7, 25). If glomerular filtration occurs at all in such kidneys, the filtrate must to some extent penetrate into the interstitial tissue. As an explanation of oliguria, this is as dubious as the hypothesis of nonselective back diffusion, since it presupposes that glomerular filtration and peritubular circulation are relatively intact.

Interstitial edema with raised interstitial pressure.—Interstitial edema with raised interstitial pressure may be conceived to be the cause of the oliguria in at least two ways: by increasing the pressure in the capsular space or by

impeding the renal blood flow. A raised interstitial pressure in ischemic anuria is fully consistent with the biopsy and postmortem findings. However, direct measurements after clamping of the renal artery (26) have shown no increase of interstitial pressure (the experimental conditions and the resulting histological changes do not seem to be completely comparable with human cases of ischemic anuria).[3]

Shunt mechanism (*Trueta shunt*).—In rabbits the renal cortex can be rendered ischemic by opening up arteriovenous anastomoses in the medulla (27). In man this mechanism may be the cause of the rarely seen syndrome, bilateral cortical necrosis, but in the vast majority of cases of ischemic anuria such a mechanism is unproven and unlikely. Renal vein catheterizations have not revealed evidence of functioning intrarenal shunts during ischemic and toxic anuria in dogs or man (6, 28, 29, 30).

Reduced renal blood flow.—Renal blood flow has been found as low as 10 per cent of normal in patients with ischemic anuria, as estimated by determination of the clearance and the renal extraction ratio of *p*-aminohippurate (6, 28). When the latter is greatly reduced as in these cases, there must be some reservation in accepting the validity of this technique since analytical errors become relatively large. However, the fact that the curve for flow during the period of recovery can be extrapolated through the low values is a point in favor of their validity. The recent introduction in renal research of methods involving the determination of rate of absorption for inert gases in kidney tissue has opened up new possibilities for flow measurements. The principle is that used by Kety & Schmidt (31) for measurement of cerebral blood flow by the nitrous oxide technique but other inert gases can be used, e.g. radioactive krypton (Kr^{85}) (32).

By means of the N_2O technique Conn, Wilds, Helwig & Ibach (29) studied renal blood flow in dogs after intramuscular injection of $HgCl_2$ and after transfusion of human blood. Anuria was produced in only three out of 21 dogs. The renal blood flow was essentially normal in all animals save the anuric ones in which it was reduced to 50 per cent of normal or less. Determinations of renal blood flow by means of the Kr^{85} technique have recently been carried out in patients with ischemic anuria following severe shock (30). An initial reduction of renal blood flow of from 10 to 20 per cent in three out of four cases and 50 per cent in one case is given in Table I (30).

It thus seems as if a reduction of renal blood flow accompanies acute anuria. However, the findings in case JR, Table I, in whom urine flows at such different levels as 85 and 1740 ml./24 hr. were associated with constant renal blood flow and oxygen consumption, suggest that decreased renal flow need not be the essential factor in the mechanism of anuria.

[3] In a recent investigation (30a), it has been shown that renal interstitial pressure as assessed by wedged renal vein pressure was not raised in five patients with ischemic anuria following shock. This suggests that an increased interstitial renal pressure is not involved in the mechanism of anuria.

TABLE I*

DETERMINATIONS OF RENAL BLOOD FLOW BY Kr^{85} TECHNIQUE IN FOUR PATIENTS WITH ISCHEMIC ANURIA

Case	Days after onset of		Urine flow,	Plasma urea,	Plasma creatinine,	24 hr. creatinine clearance,	Hematocrit,	E_{Pah}	$(A\text{-}R_v)O_2$	$RBF_{Kr^{85}}$, ml./100 gm. kidney/min.	$RMRO_{2Kr^{85}}$, ml./100 gm. kidney/min.
	Shock	Anuria	ml./24 hr.	mg. %	mg. %	ml./min.	%		vol. %		
MK	7	5	170	444	11.6	0.8	28	0.06	2.5	100	2.5
PV I	5	3	29	280	11.0	0.5	35	0.09	1.0	360	3.6
II	7	5	15	420	18.0	0.1	29	0.19	1.5	180	2.7
TL I	7	4	43	380	10.3	0.6	28	0.03	1.3	60	0.7
II	38	35	2800	28	0.6	92.0	27	0.84	1.0	700	7.0
JR I	5	4	85	380	11.0	1.0	25	0.11	3.0	75	2.2
II	12	11	1740	638	15.5	4.8	18	−0.03	1.7	115	1.9
III	21	20	3020	46	0.9	66.0	20	0.75	1.6	190	3.0
IV	52	51	1420	33	0.8	105.0	35	0.92	1.3	430	5.6
Normal Values (six cases) Range:								0.89–.94	0.5–1.6	350–770	3.8–7.7

* Abbreviations used in Table I are as follows: E_{Pah} = renal extraction ratio of *p*-aminohippurate; $(A\text{-}R_v)O_2$ = difference in O_2 content between arterial and renal venous blood; $(RBF_{Kr^{85}})$ = renal blood flow by Kr^{85} technique, expressed as ml./100 gm. kidney/min.; $(RMRO_{2Kr^{85}})$ = renal metabolic rate, as ml.O_2/100 gm. kidney/min.

Medical Treatment

Recent advances in treatment do not include new principles, and no therapy so far is available which can accelerate the recovery of kidney function.

Fluid restriction.—A number of authors (8, 14, 33, 34, 35) have stressed the importance of reducing the intake of fluids to maintain a steady decrease in body weight throughout the oliguric period. A rapid and marked weight loss, of about 10 per cent of body weight or more, usually accompanies the diuretic phase even in patients who have been on fluid intake limited to one liter per day (34). The rate at which the weight falls, the fact that it is not associated with clinical dehydration, and the failure to regain this weight on an unrestricted intake of water, indicates that it represents largely a loss of surplus of water.

Rapid catabolism of fat and protein usually occurs during the oliguric period and leads to an often astonishing loss of soft tissue which only becomes apparent after the onset of diuresis. This large consumption of body tissues is a source of surplus water in three ways: (*a*) water of oxidation, (*b*) liberated cell water and (*c*) relative excess of extracellular fluid volume over cell volume. The water of oxidation derived from rapid catabolism plus that derived from the 500 to 1000 kcal. usually provided daily from orally or intravenously administered carbohydrate may amount to 300 to 500 ml/24 hr. (140 ml. per 1000 kcal.). When calculated for the total period from onset to diuresis, an average weight loss of 200 to 500 gm. per day is seen in cases not related to wounds (8, 34,) while the loss in severely wounded cases from the Korean theater had a mean daily value of 1 kg. (range, 0.5 to 1.6 kg.) (35). The tissue which is lost contained an average of about 50 per cent water, and this water is released in addition to the water of oxidation. Finally, as the cell mass is reduced the extracellular volume should decrease proportionately to keep the ratio extracellular volume/cell volume at the normal value. However, apart from the fact that there are fewer cells and more extracellular fluid, the extracellular space may increase or decrease during anuria due to intra- or extracellular changes in osmolarity. While this is in general agreement with the concept that total body water increases during anuria, no agreement exists as far as extracellular fluid goes. One group claims contraction of thiocyanate space (36), while another finds expansion of inulin space (37). More determinations and other methods are necessary to elucidate what actually happens to the extracellular fluid during anuria. If the initial body weight is maintained over a period of several days the endogenously released water may augment total body water to a degree which may be significant in the development of cardiovascular and neurological abnormalities during oliguria.

To escape the danger of relative overhydration with the consequent considerable risk of pulmonary edema it is necessary to reduce fluid intake to about 0.4 to 0.8 liter/24 hr. Additional fluid is to be given if major losses from

urine, vomitus, sweat, drainage, diarrhea, etc. occur. Daily weights on a bed scale or a stretcher type bedside balance are of great value as a check on fluid requirements.

Caloric supply.—Cannulated major veins, preferably the inferior vena cava, can be used to secure an adequate supply of calories and fluid by means of slow, continuous infusion of 40 to 50 per cent glucose (35, 38, 39). If this route of supply is chosen, it is vital that the most meticulous care be taken to avoid infection and thrombosis. Antibiotics and heparin must be added to the infused fluid. The absolute immobilization of the tubing by special suture is important (38) and, finally, blood samples are not to be taken via the caval catheter. Even with all precautions taken there is a not insignificant risk of thrombus formation in the vena cava and this therapy should not be chosen unless oral feeding is made difficult by vomiting. If vomiting is no great problem, good results can be obtained in many patients by oral administration of about 500 ml. of 20 per cent lactose solution daily as sole fluid supply (40). Oral administration of an oil emulsion in 40 per cent glucose as originally proposed (41) almost invariably leads to vomiting.

Prevention and treatment of infections.—Prevention and treatment of infection with antibiotics is very important since these patients are very susceptible to infection. Penicillin can be given in very large doses without any serious risk while streptomycin and dihydrostreptomycin should only be given in small doses and preferably not at all when kidney function is reduced.

Blood transfusion, etc.—Blood transfusion during ischemic anuria is seldom indicated except in the treatment and prophylaxis of shock. Attempts to correct anemia by transfusion in anuric patients who have suffered no blood loss are potentially dangerous and will often result in pulmonary congestion or edema. Elective surgery and other procedures that may increase catabolism should likewise be avoided.

Treatment by Dialysis

Treatment by dialysis must be regarded only as a supplement to medical treatment, and overemphasis on the use of a dialyzer must not lead to neglect of the principles of medical management.

Types of dialyzers.—A considerable number of different dialyzers or ultrafiltrators, or both, are now in use in different countries. A survey of principles, types, and efficiencies has recently been given by Kolff & Higgins (42) and is outside the scope of this review.

Indications for hemodialysis.—The indications for the use of hemodialysis in ischemic anuria can not be rigidly defined, but must depend on clinical judgement in each case. The concentration of NPN, creatinine, uric acid, and other metabolites which accumulate in the blood during anuria are of only limited value in estimating the degree of and risk in uremia.

In the Renal Insufficiency Center in Korea (35) 40 per cent of the dialyses

were carried out on the indication "hyperkalemia" (plasma potassium > 7.5 m.eq./l.); 30 per cent were carried out for "uremia"; and 30 per cent were carried out for uremia accompanied by hyperkalemia. The decision to dialyze was not based on the level of azotemia but on the severity of the signs and symptoms of uremia: apathy, vomiting, neuromuscular irritability, and dyspnea. In civilian medicine hyperkalemia is of far less importance, especially when sufficient carbohydrates have been given. It is generally agreed that clinical signs and symptoms of uremia constitute the indications for dialysis while biochemical changes in most cases are of less importance. Dialysis should be carried out at an early stage and more frequently in cases wherein wounds, infections, complicating diseases, etc. have increased the catabolism, than in cases in which the kidney is the only organ injured. Knowledge of the rate of return of kidney function, determined as 24-hr. endogenous creatinine clearance, is a valuable and almost indispensable aid in deciding whether or not to use hemodialysis.

Results.—Due to the wide difference in the type of patients, the survival rates of various groups of patients treated with dialysis are not mutually comparable, nor are they comparable to the survival rates in hospitals without opportunities for dialysis.

Kolff (43) states that the best indication of the usefulness of dialyzers comes from evaluation of their use in individual patients. In the report from the Renal Insufficiency Center in Korea (35), it is found that the average survival time of patients who died with acute renal failure rose from 6.8 to 12.4 days after treatment with a Brigham-Kolff dialyzer was started. The mortality rate accompanying acute renal failure in military casualties was approximately 80 to 90 per cent before, and fell to about 53 per cent after establishment of the Renal Insufficiency Center and with the use of a Kolff-type of dialyzer. This may not seem a very impressive reduction but it must be remembered that in a series of patients such as this, the limiting factor in survival will be the severity of the attending wounds (35).

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CARDIOVASCULAR DISEASES (MEDICAL)[1]

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Rheumatic Fever and Rheumatic Heart Disease

There is an increasing number of reports attesting to the effectiveness of penicillin in the prevention of rheumatic fever. Thus Stollerman (1) noted seven recurrences in 543 patient years with oral penicillin (1.2 per cent) and four recurrences in 145 patients followed two years while receiving 1.2 million units of benzathine penicillin G monthly (2). A single dose of 600,000 units of benzathine penicillin eradicated streptococci from the throat in each of 102 patients when cultures were repeated in three weeks. A dose of 1.2 million units resulted in negative cultures in 92 of 93 patients, whereas after placebo therapy 53 of 66 cultures remained positive at the end of three weeks (3). Perry & Gillespie (4) reported clearing of streptococci from the throats of 22 rheumatic children but noted that only a little over one-half of the patients had detectable blood levels at 18 days and only one-fourth at 25 days. Toxic reactions to benzathine penicillin were noted in 2.1 per cent of 960 men receiving 600,000 units and in 5.21 per cent of 950 receiving 1.2 million units compared to 1.07 per cent of 845 patients receiving oral penicillin (5).

The value of hormones in the treatment of acute rheumatic fever remains unsettled. At the end of one year no difference could be demonstrated in 497 children divided into comparable groups which were treated by aspirin, cortisone, and corticotropin (6). Almost two-thirds of the children had no history of a previous attack or evidence of rheumatic heart disease. Treatment was begun within 14 days in 51 per cent. None of the agents resulted in uniform termination of the disease and fresh manifestations occurred during treatment in each group. Shortening of the PR interval, and disappearance of subcutaneous nodules and soft apical systolic murmurs were noted more frequently and more rapidly with the use of hormones. There were six deaths in the 497 patients. Stolzer and co-workers (7) treated 135 young adults; 52 with aspirin, 38 with cortisone, and 38 with corticotropin beginning on an average of the eighth day of illness. They could not demonstrate any superiority of one drug over the other, although fewer murmurs were noted at the end of 14 months in those treated with cortisone. Other observers feel that larger doses of the hormones, earlier treatment, and more prolonged treatment may be more effective in the prevention of rheumatic heart disease (8). At the end of treatment of 53 children followed from three to 39 months, 25 were normal, four had Grade I mitral systolic murmurs, 10 had significant mitral murmurs, two had aortic insufficiency, 12 had cardiac enlargement

[1] The survey of the literature pertaining to this review was completed in July, 1955

plus valve lesions, and four patients died. Massell (9, 10, 11) in an excellent review noted disappearance or lessening of congestive heart failure in 30 of 40 patients and a return of the PR interval to normal in 82 per cent of 66 patients while on hormone therapy. In emphasizing the importance of early therapy, he noted residual murmurs in 6.5 per cent when treatment was instituted in the first seven days, whereas residual murmurs were reported in 49 per cent when treatment was begun during the second week of illness. Chorea subsided in one to two weeks in 10 patients, three to four weeks in eight patients, five to six weeks in five patients, seven to eight weeks in one patient, and more than eight weeks in two patients; four showed no improvement and eight were improved but the time was not recorded. While the results with hormone therapy have been controversial, Ainger and co-workers (12) noted dramatic improvement in 5 of 13 attacks of chorea in 11 children.

Weinstein *et al.* (13), in a follow-up study of 167 scarlet fever patients seven years after treatment with penicillin, found evidence of rheumatic heart disease in eight (7.9 per cent) of 110 patients followed. They had diagnosed rheumatic carditis in 7 per cent in the original study on the basis of PR and QT prolongation in 10 and significant murmurs or polyarthritis in two. They conclude that penicillin may not reduce the occurrence of rheumatic carditis but suggest that it may suppress characteristic signs and symptoms, leaving the electrocardiogram as the most important diagnostic feature (while the electrocardiographic changes are important, less than one-third of patients show significant alterations).

The effects of drug therapy on mortality in rheumatic fever must be considered together with the repeated demonstration of a decrease in mortality during recent decades before and since the introduction of antibiotics and hormones. Wallace & Rich (14) analyzed data from New York City between 1940 and 1950 and noted a 74 per cent decrease in mortality due to rheumatic fever under the age of 20. Rheumatic heart disease remains the most important cardiac cause of maternal deaths. Thus Gordon (15) found that 82.4 per cent of 176 deaths in Brooklyn between 1942 and 1949 were due to rheumatic heart disease, while hypertension caused 8.5 per cent, congenital heart disease 3.4 per cent and bacterial endocarditis 3 per cent. He reemphasizes that congestive heart failure rather than the lesion itself is the significant factor in prognosis and treatment. Commissurotomy may result in a decrease in mortality during pregnancy. Mendelson (16) reported 16 patients who went through pregnancy without difficulty following valvuloplasty. From the literature he reviewed 40 patients subjected to surgery at the second to the thirty-sixth week of pregnancy and all but two survived and did well.

The selection of patients for mitral commissurotomy largely depends upon the presence of signs or symptoms of progressive pulmonary engorgement and the overwhelming majority can be evaluated satisfactorily by simple clinical means without resort to catheterization or other special procedures, although numerous techniques have been introduced to improve

diagnostic accuracy. Björk *et al.* (17) have attempted to differentiate predominant mitral insufficiency from stenosis using the form of the pulmonary capillary tracing during the Valsalva maneuver. Owen & Wood (18) suggest that there are differences in the "wedge pressure" curves in mitral stenosis as compared to mitral insufficiency. The electrokymogram has been utilized by Fleischner *et al.* (19) in a series of 15 patients (it is of limited value since tight mitral stenosis may cause a systolic pulsation of the left auricle). The kinetocardiogram utilizing precordial displacement has been reported by Eddleman *et al.* (20) to give significant differences in the curves of insufficiency and stenosis. Harvey *et al.* (21) point out that myocardial insufficiency rather than mitral block is the main cause of disability in some patients with mitral stenosis. This is more likely to occur in the presence of larger hearts with relatively little pulmonary hypertension, and a fixed or subnormal cardiac output with exercise. They do not recommend surgery for patients with mitral stenosis who have only mild degrees of pulmonary hypertension. Fowler *et al.* (22) found the presence of right ventricular hypertrophy, as evidenced by an R/S ratio greater than one and delayed intrinsicoid deflection of 0.03 sec. or more at V1, of help in estimating pulmonary hypertension. Thus electrocardiographic right ventricular hypertrophy was almost consistently present when the right ventricular pressure was greater than 42 mm. mercury. Scott and co-workers (23) studied 32 patients with mitral disease of whom 17 had "pure" mitral stenosis. Nine of 17 had right ventricular hypertrophy and two had incomplete right bundle branch block in electrocardiograms. These showed a marked increase in pulmonary vascular resistance in excess of 1,000 dynes sec. $cm.^{-5}$. It was noted that the pulmonary vascular resistance might be much higher without electrocardiographic evidence of right ventricular hypertrophy if there were associated mitral insufficiency or aortic valve disease. In a study of 50 patients with preoperative catheterization and biopsy of the lung at the time of commissurotomy, there was found to be no close correlation between the degree of pulmonary vascular resistance and the degree of pathologic change in the lungs, suggesting that vasoconstriction is an important factor in producing pulmonary hypertension (24). Similar studies in 23 patients showed that about one-third had hypertrophy of the media of the muscular branches of the pulmonary artery and there was a positive correlation in general between the degree of vascular disease, pulmonary resistance, and mean pulmonary artery pressure in the more severe cases of pulmonary hypertension. In reviewing 75 resected atrial appendages, thrombi were noted in 36 per cent and rheumatic myocarditis manifested by Aschoff bodies in 28 per cent. There was no clear-cut correlation between rheumatic activity and elevated sedimentation rates and the authors conclude that it is impossible to determine in advance that rheumatic fever is active. It is of interest that one-half of the patients with Aschoff bodies had good to excellent results following commissurotomy (25).

Likoff *et al.* (26), using radioactive iodinated human serum albumin,

found the blood volume elevated in patients with mitral stenosis and congestive heart failure. By contrast, those without heart failure had normal values. As would be expected, the morbidity and mortality were increased in those with elevated blood volumes. In determining the effectiveness of commissurotomy at the operating table, the fall of the mean left atrial pressure has been helpful in predicing improvement. Yu *et al.* (27) noted an average fall of 10 mm. Hg immediately after commissurotomy in 25 patients. Others have used the mitral filling pressure gradient, using direct puncture of the left auricle and left ventricle with the recording of simultaneous pressures. Normally the gradient approaches zero but it is high in mitral stenosis. When the pressure gradient remains high after valvuloplasty, it indicates inadequate relief of the obstruction. This procedure has been suggested for the determination of the recurrence of stenosis, and in selected instances in the differential diagnosis of mitral stenosis (28).

The detection of clinically significant mitral insufficiency is difficult. Mitral systolic murmurs are often present with pure stenosis, as noted by Janton *et al.* (29) in 30 per cent of 200 such patients. Only 6 of the 200 had grade III systolic murmurs and none had grade IV murmurs. By contrast a grade III–IV systolic murmur was heard in 13 of 15 patients with a grade III–IV regurgitant jet. Left ventricular hypertrophy in the electrocardiogram is seldom seen with mitral insufficiency plus mitral stenosis. The authors conclude that the absence of right ventricular hypertrophy in the electrocardiogram in the presence of mitral stenosis does not suggest mitral insufficiency. On the other hand nine of 15 patients with "pure mitral insufficiency" had right ventricular hypertrophy; 98 of 200 patients with pure mitral stenosis had no evidence of right or left ventricular hypertrophy in the electrocardiogram. Patients with predominant mitral insufficiency complain early of easy fatigability rather than dyspnea, are less prone to form thrombi in the left auricle (four in 47 as compared to 86 of 200 with mitral stenosis), and are less subject to peripheral arterial embolism (6.4 per cent as against 23.5 per cent).

Tricuspid insufficiency may produce a systolic murmur which may be readily confused with mitral insufficiency. However, less than one-half of patients with this lesion may have a systolic murmur and the deep systolic jugular venous pulsation is a more reliable sign of tricuspid insufficiency. Sepulveda & Lukas (30) found hemodynamic evidence of tricuspid insufficiency in 60 of 140 patients with predominant mitral stenosis. They noted a plateau in the trace of the pressure curves in the right atrium during ventricular systole. Tricuspid stenosis may be improved by commissurotomy and Kossmann (31) has reported two cases with an opening snap similar to that of mitral stenosis, except that the sound is heard over the lower sternum or to the right of it.

Simon & Liu (32) noted mitral systolic murmurs in 62 per cent of 24 cases of calcification of the mitral annulus. One out of four had associated calcification of the aortic valve. This condition is more common after the

age of 50, is occasionally associated with A-V block and apical diastolic murmurs, and may be confused with rheumatic heart disease.

Atherosclerosis and Coronary Disease

Atherosclerosis and its complications continue to be a leading cause of death. Much investigative work is being done concerning the etiologic relationship between atherosclerosis, circulating cholesterol, quality and quantity of cholesterol present, and the cholesterol-phospholipid ratio.

To control the role of cholesterol in the pathogenesis of atherosclerosis, attempts have been made to lower the plasma cholesterol levels by the administration of plant sterols, which compete with cholesterol for absorption from the gastrointestinal tract. Best and co-workers (33) administered beta sitosterol to human subjects on unrestricted diet and noted significant decrease in serum total cholesterol. A reduction in the cholesterol-phospholipid ratio occurred, principally related to lowering in cholesterol in as much as lipid phosphorus was not consistently altered. In three subjects studied a reduction in the S_f 10–100 lipoproteins was observed. The mechanism by which sitosterol interferes with absorption of cholesterol has not been clearly defined. The authors emphasize the importance of administering the material immediately before meals, facilitating admixture of the plant sterol with cholesterol in food and that in bile. No toxic or unpleasant side effects were observed, and it is the authors' opinion that it is suitable for long-term administration.

Barber & Grant (34) report suggestive, though not significant, decrease in the mean serum total cholesterol in 24 of 26 patients following the daily administration of nine grams of sitosterol in divided doses. At a later date each of six patients given 6 gm. sitosterol before each meal had a rapid and consistent decrease in serum cholesterol. One patient with a decrease in the serum cholesterol following sitosterol therapy nevertheless died of further myocardial infarction.

Not only is the quantity of cholesterol important, but the quality of the material is also of interest. Friedman & Byers (35) have demonstrated that exogenous cholesterol exists in the blood for a time in a different physicochemical state than endogenously derived cholesterol and is handled by the rat liver differently than endogeneously derived cholesterol. The authors point out that the arterial wall is exposed in the one case to a particle, and in the other to a molecule or ion. The hepatic reticulo-endothelial system of the rat plays an important role in the disposition of exogenous cholesterol but apparently is not involved in the synthesis or disposition of endogenous cholesterol.

The greater incidence of coronary atherosclerosis in the male below 50 years of age as compared with the female of the same age group has been a subject of interest. Studies have indicated that estrogenic therapy produces changes, generally considered to be desirable, in the serum lipid pattern of patients with coronary artery disease. Steiner *et al.* (36) found in five of 10 experimental periods that the oral administration of 0.25 to 1.0 mg. of

ethinyl estradiol daily to patients with coronary arteriosclerosis and to control patients produced a significant fall in cholesterol-phospholipid ratio, with lowering of the serum cholesterol levels but without much change in the phospholipid level. In five other periods the fall in the ratio was due to an increase in phospholipid levels without significant changes in the concentration of cholesterol. Serum neutral fat levels increased in eight of the 10 periods studied. The toxic effects of estrogens prohibited their prolonged use except as an investigative tool. There was no change in the incidence of chest pain or in the electrocardiogram in the atherosclerotic patients during the period of observation. Although during periods of estrogen administration the serum cholesterol and phospholipid levels tend to approach those seen in young healthy adults, the authors conclude that further work will be required to demonstrate that this shift improves the prognosis of patients with coronary atherosclerosis.

Stamler *et al.* (37) have shown that endogenous estrogen secretion of egg-producing hens has a prophylactic effect against cholesterol-induced coronary atherosclerosis. Estrogen-treated roosters exhibit a similar protection against the disease. Their findings lend further support to the earlier presumptive conclusion that estrogens are helpful in protecting postmenopausal females against coronary atherosclerosis.

Cholesterol is associated with all the serum protein fractions, but by far the greatest concentration is attached to alpha and beta globulin fractions. Oliver & Boyd (38) studied the distribution by zone electrophoresis of cholesterol between alpha and beta lipoproteins in 50 men with coronary atherosclerosis and in 50 healthy men. The ratio of cholesterol attached to the alpha lipoprotein to that attached to beta lipoprotein was significantly lower in the presence of established coronary sclerosis. The behavior of the serum lipoproteins in diffuse atherosclerosis has not been reported, and it cannot be said that the patterns described in coronary atherosclerotic disease occur also in predominant cerebral or peripheral arteriosclerosis.

The alpha toxin of *Cl. welchii*, a potent lecithinase, has been observed to disrupt serum lipoproteins, causing intense turbidity in the serum. Horlick (39) studied 50 patients with coronary atherosclerosis and observed early turbidity (less than 4.5 hr.) in 72 per cent of the cases, while a similar phenomenon occurred in only 22 per cent of the control group of normal individuals of similar age and in 21 per cent of normal young subjects. The study suggests that, in the group with coronary atherosclerosis, the lipoproteins are most amenable to disruption by lecithinase and possibly less stable than in the control group.

Soffer & Murray (40) studied seven patients with essential hyperlipemia and observed objective and subjective evidence of premature atherosclerosis in four of the group. Intravenous heparin produced a dramatic though transient lowering of the total lipids, due to its effect on neutral fat. Cholesterol and phospholipid showed only minimal change.

Stamler and co-workers (41) studied the effect of cortisone, hydrocortisone, and corticotropin on lipemia, glycemia, and atherogenesis in choles-

terol-fed cockerels. Despite steroid-induced diabetes and enhancement of hypercholesterolemic hyperlipemia by hydrocortisone administration, there was no intensification of arteriosclerosis of the aorta or coronary arteries. Similar results were observed with long-acting corticotropin. In contrast to hydrocortisone and ACTH, cortisone apparently intensified both coronary and aorta atherogenesis without significantly influencing lipemia or other metabolic functions in the avian species.

Agress and co-workers (42) report the presence of elevated levels of serum glutamic oxalacetic transaminase in the presence of myocardial infarction in dogs involving as little as 10 per cent of the myocardium. The peak levels were noted in 9 to 23 hours after infarction and there was a linear relation between the amount of infarction and the peak levels of transaminase. LaDue & Wroblewski (43) found elevations of 2 to 20 times normal in 49 of 50 patients within three days of transmural infarction (this offers a means of detecting muscle necrosis in the presence of left bundle branch block, or with prolonged pain and a normal electrocardiogram). Cortisone has been previously reported to reduce the size of infarcts (44). However, Hepper and co-workers (45) could not confirm these findings. They found delay in healing at four, six, 12 and 21 days, but at 60 days both the treated and untreated infarcts appeared to be equally well-healed and of comparable size.

Vakil (46) emphasized the slow up and down movement of the chest wall in 20 patients with ventricular aneurysm. Other findings were displacement of the apex impulse (50 per cent), myotonic cardiac impulse (65 per cent), double or reduplicated impulse (20 per cent), wavy impulse (30 per cent), heaving left costal margin (10 per cent), stony dullness over precordium (45 per cent), and a loud, long, musical "cooing" systolic-diastolic murmur (25 per cent).

Schlichter *et al.* (47) assembled data on 102 proved cases of ventricular aneurysm. The site of the aneurysm was as follows: (*a*). Apex of left ventricle 42.6 per cent; (*b*). Entire anterior wall of left ventricle 15.8 per cent; (*c*). Posterior basal wall of left ventricle 25.8 per cent; (*d*). Interventricular septum 12.0 per cent; (*e*). Right ventricle 1.0 per cent; (*f*). Right and left ventricles 2.8 per cent. Mural thrombosis was noted in 53.9 per cent, as compared to 21.2 per cent in myocardial infarction with thrombus formation but no aneurysm. Thromboembolism resulted in 21.6 per cent of deaths and was an important contributing factor in 13.7 per cent. Within three years 73 per cent of patients died and within five years 88 per cent. Congestive heart failure occurred in the terminal stages in 70 per cent and was the main cause of death in 48 per cent. Myocardial infarction was responsible for death in 55.9 per cent. Rupture of the aneurysm did not occur in any case. Fifty-eight patients received inadequate (three weeks or less) or no bed rest. Only 24 developed aneurysm with adequate bed rest (four to six weeks). Other factors in the etiology were extensive through-and-through infarction and hypertension existing after infarction. The authors suggest at least four weeks' bed rest for patients having through-and-through infarcts.

Linko (48), in reviewing factors determining the prognosis early in in-

farction, emphasizes the importance of shock. Thus the early mortality rate in 320 patients was 24.4 per cent. About one-third of the patients had shock, and, in this group, the mortality was 53.6 per cent. In the absence of shock the mortality was 7.2 per cent.

Baker *et al.* (49) evaluated the risk of major surgery in 70 patients with history of previous myocardial infarction undergoing 111 operations and noted a mortality rate of 3.6 per cent with 7.2 per cent cardiorespiratory complications. The latter were more frequent in those with congestive heart failure and cardiac arrhythmias. Wasserman and co-workers (50) were impressed that one-half of a group of 25 patients with postoperative myocardial infarction did not complain of pain. They cite previous cardiac enlargement, hypertension, angina, conduction disturbances, and congestive heart failure as increasing the possibility of myocardial infarction. They rightly emphasize the importance of prevention and prompt treatment of hypotension. Antonius *et al.* (51) report myocardial infarction in a 36-year-old normotensive pregnant women in the seventh month with an uneventful recovery. In reviewing the literature, they found that seven of eight patients with acute myocardial infarction recovered, and conclude that interruption of pregnancy is not warranted except for obstetric indications. Persistent musculoskeletal pain in the precordial area or anterior chest wall following infarction was recorded in 8 of 60 patients by Edwards (52). The pain was reproduced in all but one by raising the arms or the head or twisting the body, and six of eight had localized areas of muscle tenderness but the pain could not be reproduced by pressure.

Scherf & Golbey (53) decry the use of the term "coronary insufficiency" and point out that, when prolonged pain occurs, muscle necrosis is present. While there may be ST segment depression, there may be only T wave inversion and occasionaly ST elevation. They plead for establishment of the etiology of "coronary insufficiency"—angina on effort, premonitory syndrome of infarction, small or large infarctions, ectopic tachycardia with or without post-tachycardia T wave abnormality, internal hemorrhage, or acute hypertension such as with pheochromocytoma. Coronary insufficiency is not a disease entity but rather a pathophysiological state which should carry a qualifying description. This article (53) should be read by everyone who manages patients with coronary disease. The term coronary insufficiency has too long been used as a waste basket for patients having myocardial infarction without characteristic electrocardiographic changes. About 15 per cent of patients with myocardial infarction at autopsy had shown no diagnostic changes in the electrocardiogram. The therapeutic implications, with the use of modified bed rest with or without the use of anticoagulants, are obvious.

Russek, Zohman & Dorset (54) tested 16 drugs used as vasodilators and found that only glyceryl trinitrate, papaverine, and pentaerythritol tetranitrate (Peritrate) were effective in ameliorating the changes in response to exercise tests. Kalmanson *et al.* (55), on the other hand, could not demonstrate with the double blind method any beneficial effect of Peritrate in the treatment of 23 patients with angina pectoris.

One of the most significant advances in the management of the severely incapacitated patient with angina pectoris has been the use of radioactive iodine. Blumgart *et al.* (56) reviewed the results of treatment of 1,070 patient in 50 clinics; 75 per cent of 720 cases of angina pectoris showed worthwhile improvement and 60 per cent of 350 patients with congestive heart failure were improved.

Kohn *et al.* (57) reviewed 79 cases of atrial rupture from the literature and added one case of their own. Atrial trauma was responsible for 19 cases, atrial infarction, 10, fatty degeneration, seven, valvular heart disease, five, tumors, three, and 33 were inadequately studied. Wilson & Knudson (58) were able to make an antemortem diagnosis of atrial infarction in a 31-year-old male by the presence of changes of the P-Ta segment of the electrocardiogram.

Chandler & Rosenbaum (59) treated a patient with Stokes-Adams syndrome using 0.2 mg. isopropylarterenol (Isuprel) subcutaneously, and the idioventricular rate rose from 24 to 45. However, 2.0 mg. intramuscularly resulted in transient ventricular tachycardia. It was effective in preventing attacks when given slowly intravenously, using 1.0 mg. Isuprel in 200 cc. of 5 per cent glucose. Robbin *et al.* (60) studied four patients with Stokes-Adams attacks and are of the opinion that epinephrine is the treatment of choice for asystole, while Isuprel is the drug of choice when the basic mechanism is ventricular tachycardia or ventricular fibrillation and when asystole alternates with these.

Bellet and co-workers (61) used molar or half-molar lactate solutions intravenously and noted a return or an increase of the ventricular rate in five cases with complete heart block and one case of cardiac arrest. The intraventricular conduction improved with a shortening of the QRS interval. The heart beat was restored in one patient when epinephrine, ephedrine, and atropine had been ineffective. McLemore & Levine (62) subjected seven patients with complete heart block to cholecystectomy for gallstones. Five of the seven had Stokes-Adams attacks and improvement was noticeable in all following surgery. Cortisone may at times cause a disappearance of heart block, even when due to coronary disease [Prinzmetal & Kennamer (63)].

Hypertension

Hypertension due to unilateral renal disease has heretofore been largely a matter of academic interest, since the number of patients with favorable response to nephrectomy has been discouragingly small. Renewed interest has resulted from the realization that an anomalous renal blood supply may cause hypertension due to the Goldblatt mechanism, which is reversible by nephrectomy. Howard (64) reported seven patients in whom cure or striking amelioration of hypertension followed removal of the kidney. He emphasizes that a history of previously unexplained abdominal pain followed by hypertension should arouse suspicion of a renal vascular insult. Routine tests of kidney function including pyelograms may be normal, although occasionally

the involved kidney may be slightly smaller. Excretion of sodium and water by the affected kidney may be significantly reduced. Aortograms are essential to demonstrate the diminished renal supply. Similar cures have been reported by Imber & Clymer (65), Pastor *et al.* (66), and Bourne (67). Ehrlich *et al.* (68) reported malignant hypertension with death due to cerebral hemorrhage in a 32-year-old female nine weeks after sudden abdominal pain ascribed to thrombosis of a renal artery. Miller *et al.* (69) reviewed the reactions to renal aortography and noted (*a*) renal damage by direct trauma and (*b*) toxic reactions to the drug (aortography is hazardous in the presence of renal insufficiency and may cause renal shutdown).

Arterial infarction of the kidney due to thrombosis or embolism may produce acute hypertension. Teplick & Yarrow (70) stress the following clues to infarction of the kidney: no function by intravenous pyelograms, normal retrograde pyelogram with normal sized kidneys, and characteristic changes in the aortogram. These criteria may hold for massive infarction but small infarcts may be associated with normal pyelograms or with some decrease in size of the involved kidney.

Schroeder and co-workers (71) reported a followup of 106 patients with malignant hypertension treated by hexamethonium and 1-hydrazinophthalazine (Apresoline). Those with uremia invariably died and, in those with severe renal insufficiency, the hypertension was usually irreversible. Excluding the patients with uremia, the gross mortality was 23 per cent in 15 to 36 months. Of 28 who discontinued treatment 25 died of hypertensive complications. Of 68 who continued treatment, 14 died, three of hypertensive complications. While 22 patients had congestive heart failure before treatment, no deaths occurred from congestive heart failure while on the drug. Albuminuria disappeared in 41 patients and slow improvement of renal function was not uncommon. There were four deaths due to interstitial fibrosis of the lungs, attributed to hexamethonium. One of the distressing side effects of Apresoline therapy has been angina pectoris. Stein & Hecht (72) attribute this to the increase in cardiac output which they noted with Apresoline in each of 18 patients. Rowe *et al.* (73) found an average increase in cardiac output of 27 per cent in 11 patients with hypertension. The coronary flow increased 34 per cent, the coronary vascular resistance dropped 35 per cent, and the arterial-coronary sinus oxygen difference decreased 27 per cent.

The Rauwolfia preparations are widely used. Studies comparing reserpine, Raudixin, and alseroxylon derivatives have shown no significant differences in response (74). These agents are mildly hypotensive, producing an average mean blood pressure reduction of 35 mm. Hg. Moyer and co-workers (75) treated 40 patients with Roxinil, an extract of Rauwolfia containing multiple alkaloids, and found similar effects to reserpine and the alseroxylon fraction. Finnerty & Sites (76) administered parenteral reserpine to 192 patients with acute hypertension, either toxemia of pregnancy or essential hypertension; 44 per cent of these patients required additions of Apresoline or veratrum to produce satisfactory hypotension. Reserpine should not be

relied on in severe toxemia since $1\frac{1}{2}$ to $2\frac{1}{2}$ hr. are required for a maximum effect by vein and 3 to 4 hr. by intramuscular route. In mild to moderate toxemia 2.5 mg. Reserpine parenterally every 12 hr. was considered by the authors to be the drug of choice. Of 162 patients 91 showed an average reduction of 23 mm. Hg systolic and 19 mm. diastolic with a duration of $6\frac{1}{2}$ hr. The Rauwolfia preparations have been quite useful in patients with anxiety state accompanied by tachycardia and vasomotor instability. Grimson *et al.* (77) reported initial studies with an orally active quaternary ammonium ganglionic blocking agent in the treatment of hypertension. A single dose is effective 12 or more hours; its effect may be more consistent than that of pentolinium (Ansolysen) and a smaller dose is required.

Following the work of Smirk (78) pentolinium has to a large degree replaced hexamethonium. Freis *et al.* (79) found it to be five more times potent, the hypotensive effect lasted 40 per cent longer, constipation and bladder disturbances were less, and a more predictable response could be obtained by the oral route. Freis (80) found that office blood pressures were significantly higher than those taken in the home and warned about overdosage of ganglionic blocking agents if office rather than home blood pressures were utilized. Agrest & Hoobler (81) treated 31 patients with pentolinium and felt that the drug was safe and simple to use in the ambulatory management of the hypertensive patient. A median reduction of 38 mm. Hg in the mean daytime standing pressure was achieved.

Congenital Heart Disease

Shaffer *et al.* (82) observed cyclic changes in the pressure gradient across the atrial septum in seven patients with atrial septal defects and felt that these are responsible for arterial desaturation in these cases. The authors felt that it might be possible to differentiate patent foramen ovale from interatrial septal defect by this means. Swan and co-workers (83), using injections of T-1824, showed evidence of right to left shunts in 9 of 11 patients with atrial septal defects. Whitaker *et al.* (84) reviewed eight patients with patent ductus arteriosus with pulmonary hypertension; in five of the six the catheter passed through the ductus into the aorta and, in five, early filling of the descending aorta was demonstrated by angiocardiography. Right ventricular hypertrophy was noted in the electrocardiogram in each instance and there was associated right bundle branch block in two patients. Only one had a machinery murmur, one had a systolic and diastolic murmur, and two had no murmurs. Surgery is contraindicated when there is severe pulmonary hypertension or unsaturation of the peripheral arterial blood. Aortic lesions, either stenosis or insufficiency, occasionally occur in conjunction with patent ductus arteriosus. In one series, three had a continuous murmur to the right of the sternum, and one had a diastolic murmur of different pitch, while four others had signs of increased pulse pressure or atypical murmurs (85).

Vogelpoel & Schrire (86) have emphasized the difference in the murmurs of tetralogy of Fallot from that of pulmonic stenosis alone or combined with

an interatrial septal defect. In the former case, there is wide splitting of the second sound at the base, whereas, with the latter, the systolic component is prolonged and obliterates the aortic component of the second sound. The diminished pulmonic sound may or may not be audible. Pulmonary stenosis may be readily overlooked when there is increased blood flow due to associated defects of the auricular or ventricular septa (87).

McKusick (88) in an excellent review of Marfan's syndrome points out that it is an heritable disorder of connective tissue. About 80 per cent have ectopia lentis and lesions of the aorta such as aortic dilatation, aortic insufficiency, and dissecting aneurysm. These are more common than interatrial septal defects which have been overemphasized in the past.

Ebstein's anomaly of the tricuspid valve is associated with cardiac enlargement, clear lung fields, occasional cyanosis, right bundle branch block, occasional A-V block, frequently Wolff-Parkinson-White syndrome, and a high incidence of interatrial septal defects. Kerwin (89) made an antemortem diagnosis using catheter studies which showed a huge right atrium with an inability to obtain a right ventricular type of pressure curve until the catheter was extended far to the left of the midline near the left border.

Congenital absence of a pulmonary artery may complicate congenital heart disease. McKin & Wiglesworth (90) reported three cases and reviewed eight from the literature. It should be suspected when one lung is smaller than the other and in the presence of mediastinal shift. Flynn *et al.* (91) confirmed such an anomaly by demonstration of decreased oxygen uptake from the involved lung by bronchospirometry.

Endocardial fibrosis is a frequent cause of congestive failure in early life and Rosahn (92) states that it is the most common cause of "sudden death" in infants. He divides cases into an acute form with sudden onset of dyspnea, cough, vomiting, cyanosis, and tachycardia with death in a few weeks and the chronic form with a similar onset but protracted course. About three-fifths of patients die by six months of age and four-fifths die by one year. Congenital cardiovascular anomalies, particularly coarctation of the aorta, may occur in 10 to 15 per cent. McKusick & Cooley (93) reviewed the radiologic findings in 19 cases of anomalous pulmonary drainage and reported an additional case. They classify them as follows: (*a*) Partial return to the superior vena cava; (*b*) Partial drainage into the right atrium; (*c*) Left pulmonary veins to the right atrium via a persistent left superior vena cava and the coronary sinus; (*d*) Total drainage of the pulmonary veins into the right atrium; (*e*) Figure of eight syndromes—persistent left superior vena cava to the right superior vena cava. Cerebral arteriovenous fistula is a rare cause of congestive heart failure in the neo-natal period and Silverman (94) reported two deaths from this cause. Prenatal closure of the interatrial foramen causes hypoplasia of the left auricle and ventricle with subsequent heart failure at birth. Wilson and co-workers (95) reported two cases and reviewed 15 from the literature, and Brody (96) added two case reports.

Congestive Heart Failure

Gunton & Paul (97), using P^{32} tagged red cells, studied the blood volume in 102 patients with congestive heart failure, and found larger blood volumes than in 107 controls. With compensation there was usually a decrease in the blood volume, principally the plasma fraction, and with reappearance of heart failure the blood volume usually increased again. The blood volume changes were not related to the etiologic type of heart failure or to the amount of the edema. Some patients with heart failure have a normal blood volume.

Increases of blood volume were noted in each of 32 patients studied with albumin tagged with I^{131}. In five of 32, an increase in plasma volume occurred with compensation. The authors feel that no absolute conclusions regarding values for the blood volume in congestive heart failure are admissible on the basis of present information (98).

Burch (99) feels that increased venous tone may be more important than blood volume in the production of elevated venous pressure. He suggests that venous tone may be increased due to sympathetic venoconstrictor activity. Sharp elevation of venous pressure upon hepatic compression was noted; this was greatly decreased after giving 2.5 mg. of hexamethonium intravenously in 10 of 12 patients (100). In a study of 20 patients with hypertension and heart failure, it was found that the cerebral blood flow and cerebral oxygen consumption were normal (101).

Studies on the mechanism of intractable edema were reported by Cámara *et al.* (102). They noted that sodium restriction stimulates the adrenal cortex which in turn governs tubular reabsorption. They postulate that the failure of normal subjects to excrete sodium after ammonium chloride was due to increased activity of the adrenal cortex stimulated by preceding restriction of sodium. They felt that the mechanism of reabsorption of sodium and water was greatly enhanced in the presence of edema. Normal subjects whose water was restricted with a forced loss of water by evaporation did not show a proportionate loss of sodium. Water was transferred from the cells to the extracellular space in normal subjects but did not occur in the edematous patient.

Administration of pitressin tannate to cardiac patients resulted in the clinical picture of congestive heart failure, with an increase in the total solutes and sodium excretion in urine, or with a reduction in the serum solutes and sodium concentration (103). The changes produced disappeared upon cessation of pitressin. The addition of cortisone, after weight had been stabilized with pitressin, caused further edema and weight gain. There was no decrease in the total serum solutes or sodium concentration in the face of water retention. The authors postulate the retention of water by pitressin, and sodium retention due to cortisone, followed by water retention.

While there has been a reluctance to use ACTH and corticosteroids in the presence of congestive failure, Heidorn & Schemm (104) found the hormones

beneficial in selected cardiac patients with intractable edema, particularly in the presence of the sodium-dilution syndrome. Water diuresis occurred, presumably, because of suppression of the anti-diuretic hormone. Many of the symptoms and signs of congestive heart failure may occur in the normal pregnant patient. Humphrey-Long (105) recommends serial determinations of vital capacity in determining the early occurrence of congestive heart failure and in the differentiation of the dyspnea of normal pregnancy from that of pulmonary congestion. The vital capacity remains normal in pregnancy but decreases in the presence of pulmonary congestion. Davis *et al.* (106) produced right-sided congestive heart failure of the low-output type in seven dogs by constriction of the pulmonary artery. The administration of digoxin resulted in a decrease in the right ventricular pressure, elevation in the cardiac output in five of seven, and a striking increase in the sodium excretion.

Selzer and co-workers (107) reviewed the concept of Bernheim's syndrome and recommend that the term be abandoned. They found that normal puppies have "right ventricular stenosis," and that the normal ventricular septum in the human subject bulges into the right ventricle. They could not adduce a reason for the lack of pulmonary symptoms (the development of relative tricuspid regurgitation manifested by a deep systolic jugular pulsation is certainly an important factor in explaining the lessening of pulmonary symptoms). In a study of the arterial oxygen content in forty patients with pulmonary congestion and edema there was little correlation between presence of rales and the arterial oxygen saturation. Thus, in seven patients with acute pulmonary edema and bubbling rales, the oxygen saturation was greater than 93 per cent (108).

Bacterial Endocarditis

The importance of enterococcal infection in causing severe and resistant endocarditis is well-known. Geraci & Martin (109) felt that this infection occurred on a previously normal heart valve in more than half of a series of 33 cases. The effectiveness of combined penicillin and streptomycin treatment of enterococcal infections was demonstrated by these authors with 12 cures out of 16 patients treated. Two of the deaths occurred without antibiotic treatment, and two died of cerebral embolism. Thus, the corrected cure rate was 86 per cent, whereas 16 previous patients treated with penicillin alone had a mortality rate of 48 per cent. They recommended prophylactic treatment of all patients undergoing urologic procedures with one million units penicillin and 1 gm. streptomycin every 12 hr. beginning the day before operation and continuing until the day after the catheter is removed.

The combination of penicillin and streptomycin has been effective in the treatment of penicillin-sensitive streptococci when given for only two weeks. One series of 23 patients with organisms sensitive to 0.2 unit penicillin per cc., and another series of 23 patients whose organisms varied in sensitivity from 0.1 to 1.0 unit penicillin per cc. were effectively treated with 1.2 to

2.4 million units aqueous procaine penicillin and 1 gm. of streptomycin every 12 hr. There were nine deaths in the 46 patients, three because of cerebral embolism, one subarachnoid hemorrhage, one coronary embolism, and four congestive heart failure. There were no relapses in any of the treated patients (110).

The alarming increase in infections with penicillin-resistant strains of staphylococci has been stressed. Fisher *et al.* (111) found that 42 per cent of 12 patients had penicillin-resistant organisms. Of the group 54 per cent were cured. In five of 38 cases, the leukocyte count varied between 5,000 and 10,000, and they emphasize that a subacute course is not uncommon.

The use of bacteriostatic drugs alone in the treatment of endocarditis is to be deplored. However, occasional staphylococcal infections may be cured by the use of erythromycin, alone or combined with other drugs. Johnson & Hurst (112) reported the cure of staphylococcal endocarditis following large doses of erythromycin and oxytetracycline plus intramuscular streptomycin after no effect could be obtained by sixty million units of penicillin intravenously daily.

Newman and co-workers (113) noted that congestive heart failure and auricular fibrillation occurred early in the course of endocarditis in 25 per cent and 15 per cent, respectively, of cases. Congestive failure had no effect on bacteriologic cure but adversely affected the mortality. Thus the mortality was 74 per cent in the presence of congestive failure. Positive blood cultures were obtained in three of 52 cases when the patients were afebrile. The authors emphasize the need for new diagnostic and therapeutic criteria. In a study of 16 patients, followed 10 years after treatment for subacute bacterial endocarditis, Priest & Smith (114) concluded that adequately treated endocarditis is not as damaging to the heart as previously believed. They felt that the ultimate outlook was determined by the severity and nature of the preceding cardiac damage rather than by the residuals of endocarditis. The severity of myocarditis incident to active infection was found to play a greater role in future cardiac impairment than did residual valve damage.

The opposite opinion was held by Bunn & Cook (115) who reported cures in 33 of 48 patients. In six of the 15 deaths, perforation or rupture of the aortic valve was responsible. They indicated that aortic insufficiency and congestive heart failure after therapy carry a poor long-term prognosis. They stress aortic insufficiency and central nervous system complications as the major factors in the continued high mortality rather than bacterial resistance.

Electrocardiography

Frank (116) made an experimental study of the Duchosal "double cube," Grishman "cube," and Wilson tetrahedron, using a three-dimensional homogeneous torso model of the human subject with a dipole fixed in position in the center of the heart. He concluded that the scalar lead shapes on the Wilson tetrahedron vary by approximately 15 per cent from the torso and the Duchosal and Grishman systems vary even more.

Grant & Murray (117), in an important piece of work, presented studies outlining the distribution of the normal "Q area" of the chest in 38 normal subjects. The tracings of 187 subjects before and after infarction were analyzed by vector methods and 95 per cent of cases in which a QRS deformity was produced had Q waves of 0.04 sec. duration or more. In order for a Q wave of 0.04 sec. duration to occur it was found that the infarct must involve the septum or paraseptal area. This may explain why only a limited number of infarcts have characteristic electrocardiographic changes. Four types of deformity of the terminal part of the QRS complex were noted after infarction, two of these representing peri-infarction block.

The current theories of the displacement of the ST segment have been challenged by the work of Rakita *et al.* (118). Using simultaneous leads at the epicardial, intramural, and subendocardial regions after coronary artery ligation, they noted that the ST elevation was not confined to the injured area but was recorded in the cavity and intramural leads directly beneath the injured epicardial area. There was no ST segment depression in leads from the adjacent uninjured epicardial or intramural muscle. With injury produced at the subendocardial region, the ST segments were isoelectric at the overlying epicardium. They postulate two types of ST segment depression, (*a*) derived from the ventricular surface opposite to the injured area, and (*b*) depression occurring as a result of functional changes of unknown nature at the myocardial surface.

Posterior myocardial infarction was not diagnosed by electrocardiogram in 39 of 86 autopsied patients (119). Responsible factors were left bundle branch block in six cases, acute anterior myocardial infarction in 21, seven localized high infarctions, one old small infarct, inadequate electrocardiographic exploration in one, and unknown in three. The authors (119) point out that the changes in high posterior myocardial infarction consist solely of ST segment depression or tall T or R waves in the precordial leads (the presence of an initial positive force of 0.04 sec. or greater at V1 and V2 may give a clue to high posterior infarction). The ventricular esophageal electrocardiogram is occasionally helpful in the diagnosis of posterior infarction when diagnostic changes are not present in conventional leads. Rubin and co-workers (120) studied 64 patients who were thought to have posterior myocardial infarction, and in 7 per cent the esophageal leads demonstrated abnormal Q waves, which were not present in aVF. On the contrary, in 12 per cent with posterior myocardial infarction, the esophageal lead did not demonstrate the lesion. The authors concluded that aVF is more consistent than the esophageal lead in demonstrating posterior myocardial infarction; however, some cases showed a false positive Q in aVF which was absent in the esophageal lead. Thus, in 32 normals there were five instances of Q aVF, which measured 25 per cent of R, and two with Q aVF of 0.04 sec., and the esophageal leads were normal.

Wasserberger (121) found that 10.1 per cent of 131 Negro males showed T wave inversion in V1 through V6. All the patients were thought to have

normal hearts, and three were found to have normal pericardium at thoracotomy. The changes were consistently normalized by 10 gm. of potassium bicarbonate or potassium citrate mixture orally or by giving 20 to 30 mg. propantheline (Pro-Banthine) intravenously. These changes usually occurred in emotionally unstable individuals and were attributed to hypervagotonia. The author warns against confusion with subepicardial myocarditis, myocardial ischemia, and subacute pericarditis.

In analyzing the electrocardiograms of 62 patients with deeply inverted T in the precordial leads from V3 through V5, Pruitt and co-workers (122) found that 61 per cent had clinical evidence of myocardial infarction or severe coronary insufficiency. In four of five cases autopsied there was subendocardial infarction in the anterior or lateral wall of the left ventricle. In one instance the changes were related to constrictive pericarditis, in three to hypertension, in one to aortic stenosis, and in three no heart disease was found.

Isolated T negativity from leads in the region of the apex commonly occurs in the absence of heart disease. However, Schlant *et al.* (123) reported seven patients in whom this occurred in association with coronary disease and they recommend caution in evaluation of these changes in the face of symptoms suggestive of coronary disease.

It has been found that meperidine hydrochloride (Demerol) may induce tachycardia, particularly in auricular flutter, by blocking the vagus. Harvey and co-workers (124) found striking increases in pulse rates in five of seven patients given this drug. The rate increased from 94 to 188 and from 90 to 170 in two representative patients. The possible deleterious effects in such sharp increases in rate in patients with heart disease are obvious.

Endocardial fibroelastosis resulted in left ventricular strain in the electrocardiogram of 16 of 23 patients while right ventricular hypertrophy was noted in four instances, combined hypertrophy in three, Wolff-Parkinson-White syndrome in one, complete left bundle branch block in one and abnormal P waves in 14 (125). Marcisco *et al.* (126) correlated the electrocardiographic changes in interventricular septal defect with the right ventricular pressures. They describe characteristic changes which they feel may be diagnostic or strongly suggestive of the defect in most instances.

In applying the criteria for left ventricular hypertrophy in the electrocardiogram in 100 cases of left ventricular hypertrophy at autopsy, there were striking limitations of the methods in current use. It was found that the criteria of Sokolow & Lyon (127) and Wilson *et al.* (128) were the most accurate and, when combined, could detect 92 per cent of the group studied (129).

Miscellaneous

A new syndrome has been described consisting of malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart, cutaneous flushing, and bronchoconstriction (130). Of the

authors' 16 cases all had liver metastases, 11 had pulmonary stenosis, and two had questionable pulmonary stenosis. Five had tricuspid regurgitation and two had tricuspid stenosis. Four had asthmatic attacks, all had cyanosis, 14 had cutaneous flushing, and 11 had frequent, loose stools. The syndrome is believed to be due to the production of serotonin by the carcinoid. Significant quantities of serotonin have been recovered from the blood and urine (131).

Elster *et al.* (132) reviewed the clinical and autopsy findings of 10 cases of idiopathic hypertrophy of the heart in the age group 24 to 53. Thickening of endocardium was common, with secondary degenerative changes; mural thrombi were noted in six instances.

De la Chapelle & Kossmann (133) estimate that myocarditis is present in 10 per cent of autopsies. They emphasize that the symptoms and findings of myocarditis are not specific but may consist of vague precordial aching, palpitation, weakness, fatigue, congestive heart failure, tachycardia, arrhythmia, cardiac enlargement, systolic apical murmur, muffled heart sounds, gallop rhythm, and shock.

McAllen (134) reported two patients who developed fibrosis of the myocardium due to prolonged potassium deficiency associated with ulcerative colitis. One patient developed congestive heart failure due to these lesions. The coronary arteries were normal in both instances.

Interstitial myocarditis may produce apical murmurs and left auricular enlargement and simulate rheumatic heart disease (135). Chest pain in such patients may simulate that of myocardial infarction and, rarely, there may be electrocardiographic changes indistinguishable from those of infarction (136). Paulley *et al.* (137) report three cases of myocarditis believed to be due to toxoplasmosis.

Goyette *et al.* (138) described three instances of traumatic aneurysms of the aorta. They are usually caused by steering wheel or dashboard injuries, which result in rupture of one or more coats of the aorta with mediastinal hemorrhage.

Ask-Upmark (139) reviewed 28 cases of pulseless disease from the literature and reported two additional cases. The condition is characterized by arterial obstruction of the arteries in the upper half of the body, cerebral ischemia, increased sensitivity of the carotid sinus, visual disturbances with capillary aneurysms of the retina, and signs of systemic disease. Four cases were added by Bustamante *et al.* (140).

Mandel *et al.* (141) reported a case of dissecting aneurysm in a 20-year-old female and noted 70 cases in women under 40 in the literature. Three of 12 cases had associated coarctation of the aorta and five gave a history of hypertension. Approximately one-half of the instances of disssecting aneurysm in women under the age of 40 occurred during pregnancy.

Schechter & Ziskind (142) report 21 cases of superior caval syndrome. Six of 17 cases treated with chemotherapy or x-ray showed marked improvement. However, in those due to bronchogenic carcinoma, the results were

poor. Although the authors did not feel that there was a place for surgery, we have seen dramatic improvement following blood vessel grafting.

Goudie (143) studied 1270 cases of malignancy and found metastases to the heart or pericardium in 126 (10 per cent) of the cases. Attention was drawn to the heart in less than one out of six cases. Congestive heart failure occurred in nine, chest pain in seven, pericardial friction rub in six, and auricular fibrillation or tachycardia in eight. Bronchogenic carcinoma was the most common tumor.

Williams & Soutter (144), in an excellent review of the diagnosis and treatment of pericardial tamponade, report studies on 17 cases. All complained of dyspnea, five had cough, and nine complained of epigastric or chest pain. The authors point out the common misconceptions responsible for lack of recognition and emphasize the importance of pulsating neck veins in the upright position and pulsus paradoxus in diagnosis.

Dressler (145) compared 42 episodes of idiopathic pericarditis in 12 patients with 72 attacks of pericarditis due to the postcommissurotomy syndrome in 24 patients. He notes striking similarity in the two conditions and believes they are both of rheumatic etiology. This experience is at variance with that of most authors and the basis for a common rheumatic etiology is tenuous. Billings & Couch (146) noted two cases of calcified pericardium presumed to result from histoplasmosis. Mounsey (147) reported studies on the early diastolic sound of constrictive pericarditis in 18 patients and concluded that it was due to abrupt halting of rapid ventricular filling. In six patients the sound coincided with the nadir of the early diastolic dip in the right ventricular pressure curve.

Pulmonary Vascular Disease

Yu and co-workers (148) studied the pulmonary "capillary" pressure in various cardio-pulmonary diseases at rest and under stress. There was postcapillary pulmonary hypertension in 41 of 45 cases of mitral stenosis. There were 24 cases of precapillary hypertension, and exercise produced an increase in the pulmonary artery pressure with little change in the pulmonary capillary pressure. Exercise, on the other hand, produced a rise in both the pulmonary artery and pulmonary capillary pressure in the presence of postcapillary hypertension, as exemplified by mitral stenosis, left ventricular failure, or constrictive pericarditis. The authors feel that if the pulmonary artery pressure is moderately or markedly elevated, and the pulmonary capillary pressure is normal, one can exclude the left heart as the dominant cause of the pulmonary hypertension.

Fowler (149) studied the relations between the pulmonary vascular resistance and the pulmonary systolic, diastolic, and capillary pressures in a mixed group of 39 patients, some normal, some with mitral stenosis, cor pulmonale, or hypertensive heart disease. There was a relation between the pulmonary vascular resistance and pulmonary mean systolic and diastolic pressures, but not the pulmonary capillary pressure.

Smith *et al.* (150) found changes in the pulmonary vasculature in patients with aortic valve disease and hypertension similar to those with mitral stenosis. The medial hypertrophy of the muscular arteries was related to the increase in the left atrial and pulmonary venous pressure in patients with left ventricular failure. Atelectasis of the lungs in newborn infants may produce cor pulmonale; a loud systolic precordial murmur, cyanosis, and cardiomegaly were noted in a seven-day-old girl and in a newborn infant in two such patients (151).

Barnard (152) produced pulmonary arteriosclerosis and cor pulmonale in rabbits by repeated intravenous injections of minute autogenous blood clots. He noted endarteritis obliterans, fibroelastosis, and eccentric intimal thickening due to incorporation of clot by the intima. Atherosclerosis was not seen, and medial atrophy rather than hypertrophy was produced. He suggests that so-called primary pulmonary hypertension in the human may result from repeated minute embolism in normal people in the course of the rapid turnover of platelets, prothrombin, and fibrinogen.

Magidson & Jacobson (153) reported four chronic and five subacute cases of thrombosis of the pulmonary arteries with the production of cor pulmonale. Thrombosis was thought to occur *in situ* in at least one instance. However, four had thrombi in the ilio-femoral system at autopsy. The difficulty of differentiating pulmonary thrombosis from pulmonary embolism is well-known and it seems probable that the authors' cases were related to embolism. An instance of thrombosis of the main pulmonary artery following cardiac catheterization was reported by Nightingale & Williams (154), who emphasize the danger of "buckling" of the catheter while obtaining wedge pressures.

Wilson *et al.* (155) noted that the cardiac output in 21 patients with anoxia due to emphysema was lowered by breathing 99.6 per cent oxygen. The mean total pulmonary vascular resistance was decreased as was the mean pulmonary arterial wedge pressure. The decrease in pulmonary artery pressure was attributed to a fall in the cardiac output and diminution of the pulmonary vascular resistance.

Schwartz and co-workers (156) reported the use of acetazoleamide (Diamox) in 17 patients with cor pulmonale and noted diuresis in one-half of the trials with an average loss of 15.5 pounds after five to 12 days' treatment. The dose was usually one to one and one-half gm. in divided doses daily. Most patients developed slight acidosis.

Cerebral Vascular Disease

Millikan & Siekert (157) emphasize the intermittent premonitory events warning of possible impending thrombosis of the internal carotid artery. Attacks of unilateral impairment of motor or sensory function or both, occasional disorders of speech, and visual disturbances on the affected side are suggestive. The authors believe that the occurrence of such symptoms is an indication for anticoagulant therapy.

Siekert & Millikan (158, 159) studied 28 patients with thrombosis of the basilar artery. The most frequent complaints were vertigo, hemiparesis, which alternated from side to side, weakness of the limbs and face, dysphagia and dysarthria, and visual disturbances. They point out the importance of recognition of intermittent insufficiency of the basilar arterial system and the beneficial effects of anticoagulant therapy in the prevention of thrombotic occlusion.

Harder & Brown (160) reported an instance of embolization of the basilar artery by a pedicled thrombus with an attached atrial wall fragment in a patient with rheumatic heart disease. Berlin *et al.* (161) reported 13 cases of cerebral thrombosis due to atherosclerosis in young adults from 18 to 34 years of age. They point out the widespread reluctance to accept such a diagnosis, even though atherosclerotic coronary occlusion in young adults is well-recognized.

Anticoagulants

The place of the routine use of anticoagulants in the management of myocardial infarction remains controversial, debate occurring regarding the ability or inability to categorize patients as "good risks" in the first 48 hr. Most studies continue to show a significant decrease in mortality and in thromboembolism when the drugs are used. Thus Manchester & Rabkin (162) report favorable results in a series using a simple capillary prothrombin test. In a group of 150 patients with myocardial infarction treated with anticoagulants the mortality was 12 per cent with 6 per cent thromboembolism, whereas, of 150 control patients with infarction, the mortality rate was 28 per cent with 8 per cent thromboembolism. Among 33 "good risk" patients treated with Dicumarol [bishydroxycoumarin; 3,3′-methylenebis (4-hydroxycoumarin)] the mortality was 9.1 per cent as compared to 47 "good risk" controls in which the mortality was 12.8 per cent. The mortality in 117 "poor risks" who were treated was 12.8 per cent as compared to 35 per cent of 103 "poor risk" controls. Hemorrhagic complications occurred in 10.6 per cent of the treated group. Waldron *et al.* (163) found hemopericardium in the absence of rupture with greater frequency in those treated with anticoagulants. Without anticoagulants the incidence of rupture was 4.9 per cent and the incidence of hemopericardium without rupture was 4.6 per cent. By contrast, rupture occurred in 14.1 per cent and hemopericardium without rupture occurred in 19.7 per cent of those treated with anticoagulants.

Foley *et al.* (164) reported their experience with the long-term use of anticoagulants in 300 patients. In 85 patients treated for 3628 patient-months there were 31 hemorrhagic complications with one death. There were 113 episodes of embolism in 29 patients with rheumatic heart disease followed 765 patient-months from the first episode. On anticoagulants seven of 25 patients had 18 thromboembolic episodes in 1128 patient-months. Twenty-four patients with recurrent thrombophlebitis had 92 episodes in 2207 patient-months, whereas, 7 of 24 had one episode on treatment given 896

patient-months. Wright and co-workers (165) list the following indications for long term anticoagulants: (*a*) Multiple embolization in patients with rheumatic heart disease; (*b*) Multiple arterial occlusions, if it is believed that thrombosis or embolism is playing the causative role; (*c*) Recurrent thrombophlebitis, especially if the recurrences occur at short intervals of time; (*d*) Recurrent myocardial infarction, especially if thromboembolic complications are evident; (*e*) Idiopathic or familial thrombosing conditions; (*f*) Idiopathic and recurrent pulmonary embolism or thrombosis in which the original site of the thrombus may never be known; (*g*) Less well-defined indications such as recurrent angina pectoris and recurrent cerebral vascular spasm or small thromboses. A number of new anticoagulants have been introduced but there is none which appears to have striking advantages over bishydroxycoumarin.

Bourgain *et al.* (166) report their experience with [3-(1′-phenyl-propyl)-4-hydroxycoumarin] (Marcumar) whose action is more rapid and more prolonged than bishydroxycoumarin. Katz and co-workers (167) reviewed their experience with 2-diphenylacetyl-1,3-indandione (Dipaxin). Taylor & Wright (168) found no benefit in the intravenous administration of trypsin to rabbits given artificial preformed clots and concluded that its use was not justified in man.

Ballistocardiography

Starr (169) has given an excellent panoramic view of ballistocardiography. He feels that much physiologic information but little help can be obtained by this means in making cardiac diagnoses of anatomic type. Singewald (170) in an excellent essay emphasizes conservatism in using information gained through the use of the ballistocardiogram. Fagin & McIntyre (171) studied records of 356 subjects, 190 without clinical evidence of heart disease. The percentile incidence of normal borderline or abnormal curves was not greatly different in comparable age groups in subjects with or without clinically diagnosable cardiovascular disease. The authors point out the limitations and the causes of error of the method. It was necessary to discard 144 records because of artifacts or technical difficulties. Nickerson & Mathers (172) studied the physical properties of the ballistocardiograph and concluded that none of the machines in current use adequately corrects for distortion introduced by the body into the acceleration pattern.

Arbeit *et al.* (173) studied records in patients during acute rheumatic fever and found that the abnormalities paralleled the severity of the carditis. Mandelbaum & Mandelbaum (174) found abnormal ballistocardiograms in patients recovering from rheumatic fever and in infectious mononucleosis, lupus erythematosus, scleroderma, penicillin reactions, serum sickness, glomerulonephritis, and trichinosis. The authors feel that the ballistocardiograph, while not giving a distinctive pattern of myocarditis, may give the first evidence of functional impairment. They found abnormal ballistocardiographic patterns more often than electrocardiographic evidence of dis-

ease. They suggest than an abnormal ballistocardiogram in the face of atypical muscle and joint pains, fever of undetermined origin, fatigability, tachycardia, and elevated sedimentation rate may furnish convincing proof of myocarditis. The frequency of abnormal traces in a host of conditions such as listed would give one pause in accepting such a statement.

Simon and co-workers (175) studied the tracings of 17 habitual smokers with normal cardiovascular systems and found no change in the form of the records after smoking two cigarettes. Cossio *et al.* (176) analyzed the ballistocardiogram in 12 dogs before and after ligation of the vena cavae and noted that it was unchanged, even with the heart beating empty. The authors conclude that the ballistocardiogram is fundamentally caused by the heart action and may be due in a small measure to the circulation of the blood and peripheral factors.

In the past great weight was placed on a decrease in the I–J systolic waves in elderly normals and in those with heart disease. A decrease in these waves has been noted during expiration in patients with angina and normal persons who later developed coronary disease. Dock (177) studied lateral traces and found that in many patients a decrease in the headfoot waves is paralleled by an increase in the lateral waves; he suggested that this indicates a change in direction rather than in force and that, in most instances, this is due to tortuosity of the aorta.

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DISEASES OF THE CARDIOVASCULAR SYSTEM (SURGICAL)[1]

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The many recent developments in cardiovascular surgery have emphasized the importance of the mechanical elements in organic heart disease. Although surgery of the heart and large blood vessels is a relatively new and rapidly expanding field, it is based upon the solid foundation of more exact knowledge of fundamental physiologic principles. Currently, surgery offers to a large measure the means to mechanically correct mechanical defects and herein lies both its strength and its weakness.

It must be recognized that not all organic heart disease is associated with a primary mechanical defect, and that, even when such a defect exists, secondary myocardial changes may occur after prolonged periods of time. Under these latter circumstances major deficiencies of cardiac function may still remain even when the mechanical element is corrected. Furthermore, it is not possible to assume in all cases that because a mechanical lesion exists that it must be solely responsible for a given patient's signs and symptoms. All of these factors must be carefully weighed in the evaluation of each patient for operation. It is, however, extremely heartening to review the ever-increasing list of lesions for which satisfactory surgical corrections are available. A consideration of these will show that there is gradually being accumulated an imposing group of procedures which are available in properly selected cases for almost all defects. Much still remains to be done in extending the scope to a wider selection of patients and to make all of the procedures definitive. On the basis of the progress already made it would seem to be assured that rapid strides will be made in this direction.

The primary principles of the surgical management of cardiovascular diseases have become sufficiently well-defined that the possible benefits of operation should be considered in all patients with organic cardiovascular disease associated with shunts, obstructive or valvular lesions.

Patent Ductus Arteriosus

The surgery of patent ductus arteriosus has become well-standardized since the development of the division and suture technique by Gross (1, 2) and the multiple ligation technique by Blalock (3). These methods have been almost universally adopted and yield definitive closure with minimal mortality rates. Operation is advised in all patients over the age of two when the diagnosis is made. Operation is not denied any patient purely on the basis of age if there is any good indication for operation.

The diagnosis of patent ductus is associated with the characteristic

[1] The survey of the literature pertaining to this review was completed in December, 1955.

murmur in approximately 95 per cent of the patients. Particular attention has recently been directed toward the diagnosis of the atypical ductus arteriosus in which the usual murmur is modified (4). Alteration of the murmur may be caused by the angle at which the ductus traverses from the aorta to the pulmonary artery or by the relationship of the pressures in the pulmonary artery and aorta. The co-existence of another lesion, such as tetralogy of Fallot or coarctation, also may increase the difficulty of the diagnosis. In the evaluation of such unusual situations it is important that the entire physiologic mechanism be evaluated by catheterization to determine whether or not the ductus is associated with increased, normal, or decreased pulmonary flow. It is quite apparent that when the ductus is associated with tetralogy of Fallot it exists as a compensatory mechanism and the ductus should not be divided unless definitive correction of the tetralogy is to be accomplished. If the patent ductus exists in association with coarctation, the lesion should be corrected early in life (5, 6).

There has been a renewed interest in the rarer forms of patent ductus in which there is a reversal of flow through the ductus so that the shunt is from right-to-left rather than left-to-right as is usually the case. Complete reversal of the shunt tends to be characterized by cyanosis of the lower extremities without cyanosis of the upper extremities or with less cyanosis in the upper extremities than in the lower. When the pulmonary hypertension resulting from the ductus is associated with pulmonary artery endarteritis with extremely high resistance to pulmonary flow and an absolute decrease in pulmonary blood flow, closure of the ductus cannot be expected to be helpful (7). If calcification of the pulmonary artery occurs in the presence of a reversal of shunt, the technical difficulties in closure of the ductus may be extremely great. Operation is not advised when there has been permanent reversal of the shunt.

Other cases have been recognized in which the flow through the ductus is only transiently reversed or in which the pulmonary resistance does not appear to be fixed at a high level. In these instances operation, though difficult, may give good improvement.

Coarctation of the Aorta

It has now been ten years since Crafoord & Nylin (8) and Gross & Hufnagel (9) reported the first successful operations for coarctation. Resection of the area of constriction with end-to-end anastomosis is the procedure of choice. When the area of stenosis is too long to permit direct approximation of the ends, the defect may be bridged by an aortic homograft or by a plastic prosthesis of cloth. The optimum age for operation is from 8 to 12 years of age, but is sometimes necessary in infancy (10 to 12).

As experience has been accumulated, aneurysms distal to the area of coarctation have been found with increasing frequency. Most often these have been unsuspected preoperatively on clinical evidence and some have not been demonstrated even though aortography has been done. Age per se is no bar to operation. The use of grafts and prostheses has almost eliminated

the previously existing problems associated with the long areas of obstruction or aneurysm (13 to 17). Operative mortality has constantly decreased and is now well under 5 per cent in the uncomplicated case.

Pulmonic Stenosis

Anatomical and pathological studies have given a new basis for understanding variations of pulmonic stenosis (18 to 20). Pulmonic stenosis may be associated with persistence of the foramen ovale or a true inter-atrial septal defect. The stenosis may be valvular, infundibular, combined valvular and infundibular, or there may be atresia or hypoplasia of the pulmonary valve or the pulmonary artery. In the presence of an intact interventricular septum, treatment of pulmonic stenosis by one of the direct methods is preferable. Cutting of the valve by a transventricular approach has been most widely used (21, 22). The expandable knife is introduced through a small incision in the right ventricle and the valve can be incised in one or more planes. Following this, a dilator provides an adequate opening in most cases. Mortality rates for this procedure are very low, but the right ventricular pressures may remain elevated.

Dubost (23) advocates inserting the dilator and knife through the superior left pulmonary artery, opening the valve in a retrograde fashion. More recently, Swan *et al.* (24, 25) have suggested that operation which permits visualization of the valve is more satisfactory. After opening the pulmonary artery the top of the valvular cone is excised and two incisions are made down to the annulus, converting the valve into a bicuspid structure. This procedures is accomplished under hypothermia with complete inflow occlusion. It offers the advantage of complete division of the valve leaflets. If indirect operation is elected, it is preferable to measure the pressures in the ventricle and in the pulmonary artery before and after valvulotomy on the operating table to insure that the opening is sufficiently large to adequately reduce the pressure gradient across the valve.

Infundibular stenosis may be corrected by a transventricular punch resection as advocated by Brock (26) or by a direct vision resection of the infundibular stenosis utilizing a right ventriculotomy under hypothermia. Closed transventricular resection has had a low mortality rate. Direct operation with the open ventricle offers obvious advantages and undoubtedly will be more and more widely used, but sufficient experience has not yet been accumulated to fully evaluate its risk (27 to 29).

Operation is, if symptoms are present, advised in the pure valvular lesion when ventricular pressures are over 80 mm. of mercury. It is generally agreed that patients with ventricular pressures of over 100 mm. of mercury should be advised to have operation even in the absence of symptoms.

Tetralogy of Fallot

Surgical treatment of tetralogy of Fallot is currently in a state of change. The brilliant work of Blalock & Taussig (30) and of Potts *et al.* (31) in the correction of tetralogy of Fallot with shunting operations has produced ex-

cellent results. The fundamental physiologic objections to these procedures have long been recognized, but the technical difficulties of the more direct and completely corrective measures have prevented their adoption. New methods are now becoming possible so that the choice of the best procedure is important.

In tetralogy of Fallot valvular stenosis occurs in approximately 10 per cent of the patients, infundibular stenosis in approximately 50 per cent, and combined valvular and infundibular stenosis in about 20 per cent; pulmonary hypoplasia or atresia occurs in 20 per cent (32). It is, therefore, helpful to determine the anatomical lesion as accurately as possible preoperatively if one is to make a rational choice of the optimum method for correction.

Potts (33) has summarized his experiences with shunting operations for cyanotic heart disease in over 500 patients. When operation was necessary in the age group of two weeks to three years of age the mortality was 15 per cent. Over the age of three years it has approximated 3 to 4 per cent. In the follow-up on 100 patients 68 per cent had good results, 16 per cent had fair results, one was unchanged, and five had died of various causes after intervals from six to eight years. He advises aortic pulmonary anastomosis on the left side, if the arch curves to the left, and a subclavian pulmonary artery anastomosis on the left, if there is a right aortic arch present.

Brock (34) has been an advocate of the direct attack in tetralogy of Fallot. He advises infundibular resection if infundibular stenosis is present, and valvulotomy if valvular stenosis is present. Approximately 87 per cnet of his patients have improved. The mortality rate has approximated 13 per cent.

There is general agreement that infants who require operation early in life because of severe symptoms may derive great benefit from a shunting operation, particularly in the presence of pulmonary artery hypoplasia or atresia. There is, however, an increasing tendency to perform direct operations, such as infundibular resection or valvulotomy, or both, in older children. With each of these procedures the ventricular defect and the over-riding are not corrected, but the flow of blood to the lungs is increased. It has also been noted that if the obstruction is too completely removed, excessive pulmonary pressures may develop in the presence of an interventricular defect.

The ideal operation is correction of the obstruction to the pulmonary blood flow and closure of the interventricular septal defect with exclusion of the aortic root from the right ventricle. This can be accomplished by right ventriculotomy under hypothermia or hypothermia plus cross-circulation or the use of an artificial heart-lung apparatus. In infants this can be also performed with the use of arterialized blood propelled by a single pump and simultaneous removal of blood from the venous side. The mortality rate with this method is still extremely high, but it offers promise of being the method of election in the future (35, 36).

Atrial Septal Defect

Atrial septal defects are being recognized with increasing frequency and the characteristic picture of this lesion is becoming more widely recognized (37). Patients who have a significant left-to-right shunt associated with symptoms, particularly if the pulmonary flow is three or more times that of the systemic flow, are advised to have operation. If, however, there is extreme pulmonary hypertension with high pulmonary vascular resistance and a small left-to-right shunt, the optimum time for operation has been lost. If the patient has a right-to-left shunt without an increase in pulmonary blood flow, operation is contra-indicated.

Many anatomical studies have been of value to the development of methods for the indirect closure of inter-atrial septal defects (38). The recognition of ostium primum and ostium secundum defects pre-operatively is of great help. Ostium secundum type of lesion tends to be relatively amenable to surgical treatment, while those of the septum primum type offer greater difficulties. There are in all such congenital lesions many variations, including transposition of the pulmonary veins and atrioventricular communis, which add to the complexity of the correction of the lesion. Bailey *et al.* (39) have utilized several variations of the method originally described by Cohn (40) which employs the redundant right atrial appendage for the closure of the defect. In this procedure the atrial wall is sutured to the edges of the defect and the wall is invaginated as each suture is placed. With various modifications of this procedure it is possible to exclude anomalous veins and to divert them from the right auricle into the left. When mitral stenosis co-exists it may be corrected simultaneously before closure of the defect (41, 42).

Lam (43) has advocated a simple method for the approximation of the anterior lip of the septal defect to the posterior auricular wall after the defect has been explored through the right auricular appendage. This has been termed an atrial wall conserving type of atrioseptopexy. Watkins & Gross (44) have devised a rubber well through which the edges of the defect can be closed, and, if necessary a patch of polyethylene sheeting or compressed Ivalon can be sutured to the edges of the defect (45 to 48).

Sondergaard (49) has utilized the anatomical separation of the atrial septa in their inferior portion, and the dissection of the groove between the right and left atria, to pass an encircling suture around the defect, closing it by a ligature. This is an extremely simple method whereby a probe can be passed along the upper margin of the interventricular septum in the plane of the base of the auricular septum. When this has been accomplished and the pulmonary veins have been dissected free from the vena cava, the suture enters at the upper margin of the septum and emerges at the lower margin just above the entrance of the coronary sinus. When both ends of the suture have emerged, the suture is then tied over a pad of muscle or gelfoam in the interatrial groove.

Open operation has been advocated by many and is accomplished under hypothermia with lowering of the body temperatures to approximately 27°C. (50 to 66). At this temperature an inflow occlusion of 7 to 10 min. is safe. The defect, which is large and tense when the heart is full of blood, becomes flaccid when blood is excluded from the heart and the edges approximate easily. Direct suture can be accomplished under vision in 3 to 5 min. The heart is filled with fluid prior to the final closure of the atrial wall incision. This method has as fundamental problems the introduction of air into the heart and the increased irritability of the heart at lowered body temperatures. It is extremely important to evacuate all air from the left heart before resumption of the circulation. The use of sino-auricular nodal block (67, 68) or the use of neostigmine greatly reduces the dangers of irritability.

The results of closure of interauricular septal defects have been excellent in experienced hands by all of the various methods which have been mentioned. The closed methods carry the advantages of the decreased risk of introduction of air, but have the disadvantage of the possibilities of incomplete closure. If closure is not complete there are few benefits from merely decreasing the size of the opening.

Ventricular Septal Defects

Closure of interventricular defects is still in the early phases of its development (69, 70). It is most readily accomplished by direct open operation utilizing some extracorporeal pumping mechanism. This may take the form of a synchronized pump with an artificial oxygenator, controlled cross-circulation, or a continuous perfusion with arterialized blood. When the necessary cannulae are in place, the right heart may be opened after placing a tourniquet around the aortic root. After mobilization or retraction of the tricuspid valve, the ventricular defect may be closed with multiple sutures. During the period of operation 20 to 40 cc. of blood per kilogram of body weight of the patient is perfused per minute. The aortic tourniquet is tightened only as necessary to insure a blood-free field during essential parts of the procedure. Using modifications of these techniques, closure of septal defects in severely ill patients can be accomplished with a mortality of 25 per cent or less. As experience has accumulated in this field it can be expected that these rates will be greatly lowered in the immediate future (71 to 78).

Mitral Stenosis

Surgical management of mitral stenosis has become increasingly satisfactory. The results which have accumulated from the many cases which have been treated during the past six years have shown that the procedure produces lasting results (79 to 92). The technical details of the operative procedure have been increasingly well-defined, and the importance of a careful and complete operation has been manifest. Mitral commissurotomy must include, if possible, complete separation of both leaflets as far as the mitral

annulus. It must also include mobilization of the chordae tendineae (93 to 100).

Numerous techniques have been described to minimize the dangers of embolization during operation, and these have been successful in lowering the incidence of this complication. The over-all mortality rate for class III and early class IV patients is well under 5 per cent. It has become more and more apparent that the majority of the so-called recurrences or poor results have primarily been due to inadequate openings of the mitral commissures at operation. In the hands of experienced surgeons the results are greatly superior to those obtained by the occasional operator.

Re-operations are being reported with increasing frequency and carry a slightly higher risk than primary operations. In the majority of these cases it is found that the valve has not been adequately opened. Many instruments have been developed to facilitate the opening of the commissures. In a high percentage of cases the use of some such adjunct to the finger will be necessary. This has been estimated as high as 75 per cent by Glover and as low as 30 per cent by others. At the conclusion of the procedure the left auricular appendage is amputated. The incidence of embolization postoperatively, even in patients who have had previous embolic phenomena, is extremely low. In the cases of relatively pure mitral stenosis excellent results can be anticipated in 80 per cent of the patients, and good results in another 10 per cent. Postoperatively, all patients should be kept on a program of rheumatic fever prophylaxis for prolonged periods of time. It should be emphasized that relief of the mitral stenosis in no way protects the patient from recurrence of rheumatic valvulitis which may lead to other valvular lesions, including those of the aortic valve, the late development of mitral insufficiency, or both. Therefore, routine prophylaxis should be the rule in the attempt to minimize this possibility. Fortunately, the late development of such lesions has been rare in the results reported (100 to 103).

Mitral Insufficiency

The correction of mitral insufficiency has been attempted by numerous methods. These have included the use of intra-cardiac slings and stents, but the over-all results have not been entirely satisfactory (104 to 121). Similarly, attempts to suture the edges of the mitral valve in such a fashion as to correct the insufficiency without the production of stenosis have been helpful only in an extremely limited group of patients. More recently, an encircling type of procedure for the narrowing of the mitral annulus which will permit the approximation of the valve leaflets has been introduced by Glover, Davila *et al.* (122, 123) for the type of insufficiency associated with valvular dilatation. This procedure utilizes a technique for the constriction of the mitral annulus with a broad tape which passes beneath the major branches of the coronary arteries and beneath the coronary sinus. When the suture is drawn taut the circumference of the mitral annulus can be decreased to a sufficient degree that the operator with his finger inserted into the left auricle

can determine the point at which the valve will close competently. The early results of this procedure appear promising.

The use of the open technique for the correction of this lesion also seems imminent (124), and appears most applicable in cases with combined stenosis and insufficiency when there is a localized absence of valvular tissue.

Aortic Stenosis

Dynamic studies of the normal and pathological aortic valve have been made by McMillan *et al.*, using the technique of motion pictures of the post-mortem heart (125). These have demonstrated the variations in the mobility of valves of different degrees of calcification and fibrosis and have further demonstrated the limitations and usefulness of aortic valvulotomy under different circumstances. With this technique one can also evaluate the mobility of the leaflets following valvulotomy accomplished by various means. These studies have shown that blind valvulotomy with a dilating type instrument usually splits the weakest commissure only and seldom more than two commissures. However, the end result of dilatation would appear to depend more upon the inherent mobility of the valve at the time of operation than upon the method used (126, 127).

The early clinical work for the correction of aortic stenosis was done through the transventricular approach, using one of several types of dilators. The Bailey dilator has probably been most widely employed. Other similar methods for the retrograde dilatation of the valve have also been employed by others (128 to 133). The results have been variable, depending upon the condition of the patient and the particular pathology of the valve. When pure aortic stenosis was present the mortality from the transventricular approach has been approximately 25 to 30 per cent. This, however, includes a considerable number of patients who are in the late stages of their disease. If only early patients are selected the over-all results tend to be significantly better and the mortality rate considerably lower. Bailey has pointed out that when both mitral commissurotomy and aortic valvuloplasty were carried out simultaneously that his results, using the transventricular route, have been distinctly better with an operative mortality rate of only 19 per cent.

The trans-aortic approach has gained increasing usefulness and a number of variations for this procedure have been suggested. Bailey uses a pericardial pouch sutured to the wall of the aorta just above the aortic valve through which digital examination of the valve can be accomplished and instrumentation carried out. Hufnagel has employed an aortic graft sutured to the wall to accomplish both digital and instrumental manipulation of the valve. A dilator may be introduced through the pouch or a large branch of the aortic graft. Many operators now more commonly employ a knife which can be inserted along the finger and the commissures separated in a manner similar to that employed in mitral commissurotomy. The over-all results in the trans-

aortic procedures have appeared better than when the blind dilatation is used.

One can accomplish a more direct and accurate evaluation of the pathology involved and can make certain that the commissures are cut more widely to the annulus when the valve can be palpated with the finger. As in all stenotic valvular surgery it is becoming increasingly apparent that, to insure maximum benefit from surgical intervention, it is important to measure the pressures above and below the valve to determine whether or not a gradient due to obstruction exists after the operative procedure has been carried out to the satisfaction of the operator. If such a gradient still exists, a decision must be made as to whether further improvement can be obtained by additional manipulation of the valve. It would appear that the consensus indicates that the incidence of ventricular fibrillation and other postoperative complications is less if the trans-aortic approach is used.

Sarnoff, Donovan & Case (134) have reported a modification of the method of apical aortic anastomosis originally proposed by Jeghers, Donovan and Hufnagel for the correction of aortic stenosis. A valvular prosthesis is inserted between the left ventricular apex and the aorta so that the obstructed aortic valve is by-passed. With the method blood is ejected from the left ventricle through a ball valve into the aorta. The valve in the system prevents back flow into the ventricle. Sarnoff has devised a simple introducer to insert the prosthesis into the ventricle which minimizes blood loss. This procedure is as yet in its experimental stages and with modifications offers possibilities for the avoidance of manipulation of the aortic valve itself.

There is general agreement that the indication for operation in aortic stenosis should not be what Harken terms the "terminal phase" of the disease (135). It is therefore imperative that, if operation is to be at all successful, patients should be selected when they show progression of their disease and before they have reached the terminal phase.

Aortic Insufficiency

The malignant course of wide open aortic insufficiency is becoming widely recognized. The greatest experience in the treatment of aortic insufficiency has been with the ball valve prosthesis, employing the multiple point fixation rings for fixation in the aorta (136 to 138). This procedure is primarily designed to relieve the major load of aortic insufficiency but does not entirely correct it. The patient who is relatively ideal for operation is the one who is under the age of 50 with free aortic insufficiency with a diastolic pressure of less than 50 mm. Hg and without other organic valvular lesions, although the murmur of relative mitral insufficiency or relative aortic stenosis may be present. All of the patients who have been offered operation have had left ventricular enlargement, some degree of congestive heart failure, and have signs of progression of their lesion either by symptoms, physical findings, or x-ray. The patient who is over the age of 50

with an extremely large left ventricle is a poor operative risk and operative mortality is high. The relatively young individual who has early signs of progression has a low risk.

Care in the selection of patients, particularly in the younger age group, is necessary to rule out those who have an acute rheumatic process, for a recrudescence of rheumatic fever in the immediate postoperative period carries a high mortality rate. The serious damage to the left ventricle which occurs with prolonged aortic insufficiency makes the surgical correction of this lesion difficult, so that for optimum results one must offer operation to patients before their disease has progressed to a terminal state.

When the myocardium has been damaged by prolonged left ventricular dilatation and coronary insufficiency, its recovery becomes questionable even after correction of the valvular lesion.

The over-all results following insertion of a plastic prosthesis are good in terms of rehabilitation of the patient. Successful operations have been performed when aortic insufficiency has been associated with mitral stenosis and with coarctation. Both lesions are corrected during a single procedure.

When left ventricular dilatation is present it can be expected to greatly decrease. Left ventricular hypertrophy, however, only slowly changes in size. Renal blood flow is improved and, in the majority of cases, the gallop rhythm and other signs of failure which have been present preoperatively have disappeared. Patients have now been followed for three years after this type of operation and the improvement which was manifest in the early postoperative period has been maintained.

Other methods for the correction of aortic insufficiency are under study, including the use of constricting annular ligatures at the base of the aorta and other intra-vascular prostheses at the level of the aortic valve (140, 141). These procedures at the present are still in the experimental phase, but offer promise for the future.

Coronary Artery Disease

Surgical treatment of coronary artery disease has had three major objectives: (*a*) the increase of arterial blood flow to the myocardium, (*b*) the prevention of ventricular fibrillation after coronary occlusion which might not otherwise be fatal, and (*c*) the relief of anginal pain. In one sense the increase of oxygenated blood to the myocardium eliminates the pain of coronary insufficiency, but some procedures are directed primarily only to the relief of pain without necessarily increasing the blood flow.

Methods for increasing flow of blood to the myocardium have included the systemic artery coronary sinus anastomosis as advocated by Beck (142 to 147) and the use of foreign substances such as talc and asbestos in the pericardium to stimulate the ingrowth of vessels from either the pericardium (148) or the lung. The use of pedicled skin grafts and the direct implantation of the systemic artery in the myocardium have also been advocated (149 to 151).

Other methods advocated by Fauteux, and Rabil *et al.* (152) have combined procedures for partial occlusion of the great cardiac vein, resection of the anterior cardiac plexus, and the increase of collateral circulation by ligation of the internal mammary artery distal to its pericardiac phrenic branch.

Each of these procedures has its advocates and it is not certain at this time as to which of them is most advantageous. It appears to be increasingly evident from experience gained by many investigators that surgical intervention can reduce the incidence of angina following operation and that it would appear that over-all life expectancy can also be increased. Careful clinical evaluation of these procedures will be necessary over a long period of time before a definitive answer can be obtained.

Obstructive Arterial Lesions

Arteriosclerosis of the vessels involving the aorta and the arteries to the extremities has long been a serious problem. With the development of methods for the homotransplantation of arterial segments and, more recently, the development of synthetic arterial prostheses it is possible to offer a direct approach to the reconstruction of diseased arteries (153 to 161). It is imperative that in the examination of the patient with arteriosclerotic disease that the examination of the patient should include a determination of the type of disease which is present, that is, whether it is vasospastic or organically obstructive. If it is obstructive, it must be determined whether the site of obstruction is in the large vessels, small vessels, or both. If large vessel occlusion is present, the site of the obstruction must be determined together with its upper and lower limits. In the presence of obstruction of major arteries, that is, arteries proximal to the bifurcation of the popliteal artery, serious consideration should be given to the possibility of direct reconstruction of that channel.

The treatment of choice in all such lesions of major arteries is the restoration of the blood flow by arterial graft or prosthesis. This may be accomplished under varying circumstances with either end-to-end or end-to-side anastomosis. Hufnagel (162) and others have pointed out that, when arterial obstruction begins above the inguinal ligament, it tends to end above this level in a very high percentage of patients.

It cannot be over-emphasized that the treatment of choice in major arterial obstruction is reconstruction of the vessel either by grafting or by endarterectomy (163 to 172). Using the techniques which are now available, good results can be expected in a minimum of 70 per cent of the patients, if the site of obstruction can be completely delineated and it exists above the level of the popliteal artery.

Arterial Aneurysm

Aneurysms of the aorta and the large arteries have previously been considered an incurable disease. With experience gained in the reconstruction

of arteries and the availability of arterial replacement this situation has completely changed. In experienced hands aneurysms both of the saccular and fusiform type can be corrected in essentially any anatomical situation, providing the condition of the patient does not otherwise preclude operation.

Aneurysms of the abdominal aorta are usually single and, in the vast majority of cases, arise below the renal arteries. These are primarily due to arteriosclerotic disease. Syphilitic aneurysms are more commonly present in the ascending and transverse thoracic aorta, and tend to be saccular. Posttraumatic aneurysms tend to arise in the area of the left subclavian artery.

In the case of abdominal aortic aneurysms, resection and replacement with prostheses or grafts can be accomplished routinely with low mortality rates. Aneurysms of the thoracic aorta are usually resected under hypothermia or with a by-pass technique during the resection.

The use of synthetic grafts in aneurysm is gaining increasing momentum and the results reported have been excellent, although technical difficulties in working with synthetic material are sometimes distinctly greater than replacement with homografts. It is well-established that untreated aneurysms of the aorta carry an extremely high mortality rate. Surgical therapy with resection of the aneurysm can be accomplished successfully in almost all cases. It is the consensus that the indication for the resection of an aneurysm is its detection (173 to 182).

Diagnosis of leaking or a rupture of an aortic aneurysm is indication for an emergency operation. Without surgical intervention leaking or rupture of an aneurysms is uniformly fatal. The sooner operation can be performed after this diagnosis is made the greater the chance of cure. Many successful cases of operation for ruptured aortic aneurysms have been reported.

Dissecting aneurysms usually arise in the proximal aortic arch. Surgical therapy as developed by DeBakey *et al.* (183) is directed toward converting the resected vessel into a single channel by trans-section of the aortic arch just below the left subclavian artery under hypothermia. Resection of the intima and the remaining media of the vessel so that the two proximal portions freely communicate with the interior of the aorta is first accomplished. Following this the distal vessel is converted into a single lumen channel by removing the intramural clot and suturing the wall into a single layer. The proximal and distal aortic segments are anastomosed. The blood can now flow freely through the proximal area of dissection back into the normal aortic lumen and no further dissection can occur distally.

This is an emergency procedure and should be done as soon as possible after the diagnosis is made.

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DISEASES OF THE GASTROINTESTINAL TRACT[1]

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A review which emphasizes the newer contributions to the field of gastroenterology perforce emphasizes many technical and laboratory procedures. Despite phenomenal scientific advances attention might well be directed to the ever greater need to pay more attention to the patient. This implies consideration of the patient's personal and financial problems and the use of common sense in the ordering of the expensive laboratory tests. Recent reemphasis of this by one of our surgical colleagues might well be required reading preliminary to this review (1).

ESOPHAGUS

Specimens for biopsy were obtained from 61 patients who had clinical evidence of "peptic esophagitis." According to Palmer (2), evidences of disease were localized largely to the lamina propria mucosa. This suggests that peptic esophagitis is not caused by corrosive action of regurgitated gastric juice. Two patients who had attempted suicide by ingesting strong chemicals, and were suffering the consequent corrosive effects, were treated early with cortisone, antibiotics, and procaine solution (3); esophageal stricture did not result. Further investigation of this technic may be warranted. Follow-up studies of 149 patients support the view expressed at various times by Harrington and others that esophageal hiatal hernia is a progressive disease (4). In 13 per cent of the cases the hernias progressed from small to large size over a five-year period, whereas those followed six or more years showed a 58 per cent incidence of progression. The large hernias were associated with significantly greater complications and 28 per cent demonstrated ulcer, esophagitis, or stricture. Esophageal reflux seems to be accompanied by changes in the intra-esophageal pressure which can be used to detect its occurrence (5). This takes place only during inspiration. The facts fit well with the conception of a mucosal valve guarding the cardia. Attention should be called to a very worth-while review by Barrett (6) of certain controversial aspects of hiatal hernia. Emphasis, again by a British worker, is on the functioning of a mucous flap in protection of the esophagus against regurgitation.

STOMACH

Gastric and duodenal ulcers may have a common etiology, but there are insufficient data to support this. The threat of cancer in the gastric ulcer and

[1] The survey of the literature pertaining to this review was completed in July, 1955.

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the almost universal lack of cancer in the duodenal ulcer necessitates consideration of these two lesions as entirely different.

Johnson (7) reports that concomitant gastric and duodenal ulcers are present in about 5 to 9 per cent of patients. The duodenal ulcer is likely to appear first. The pattern of secretion simulates that of duodenal ulcer or pyloric stenosis rather than of gastric ulcer. Of the patients with pyloric stenosis 16 per cent had gastric ulcers as well. Some years ago Kirkland and co-workers emphasized that small gastric ulcers may cause apparent pyloric obstruction. Thus it is difficult to know if the gastric ulcer is the result or the cause of pyloric obstruction.

In cats the acid and pepsin secretions during vagal stimulation are initiated by different mechanisms according to Linde (8). The secretion of acid is stimulated by neurohormonal mechanisms involving the chain acetylcholine, gastrin, and histamine, while the secretion of pepsin is stimulated directly by acetylcholine liberated by the vagus nerves.

In the dog Dragstedt *et al.* (9) found that pyloric stenosis caused hyperfunction of the antrum, gastric hypersecretion, and gastric ulcer. Gastric hypersecretion and gastric ulcer followed transplantation of the antrum into the colon of dogs. Pyloric stenosis with gastric hypersecretion may be a cause of gastric ulcer in human beings.

According to Woodward and co-workers (10), solutions of food, when applied to the isolated gastric antrum, caused secretion of gastric juice from isolated pouches of all or part of the body or fundus of the stomach. This response was inhibited when the food substances were distinctly acid. The intestinal and nervous phases of gastric secretion were not inhibited by perfusion of the gastric antrum with acid, which appeared to interfere with the formation or release of gastrin. The gastrin-producing mechanism was promptly and strongly stimulated by mechanical distention of the isolated, innervated antrum. Perfusion of an isolated segment of duodenum with tenth normal hydrochloric acid failed to inhibit the gastric secretion on feeding an animal having a Heidenhain pouch. The application of solutions of cocaine or atropine to the mucosa of the isolated antrum prevented the secretion of gastric acid in response to the application of foods to the antrum but did not prevent the secretory response to histamine. Cocainization of the mucosa of the isolated antrum did not block the nervous phase of gastric secretion.

Hypersecretion may be attributed to the inhibition of the normal autoregulatory duodenal reflex, stimulated by the presence of acid chyme (11). The reflux of alkaline duodenal juices through the gastrojejunal stoma during a Billroth II operative procedure may likewise result in hypersecretion. Lippman & Longmire (12) have reported that attempts have been made to reduce the acid secretion of the stomach of dogs by removing 30 to 90 per cent of the mucosa of the stomach and replacing it with jejunal mucosal and submucosal grafts. Work has been done by Walker, Olson & Necheles (13) to determine whether normal fasting dogs have basal gastric secretion. In 10 dogs the stomach was separated from the small intestine and the con-

tinuity was established by an external connection between a cannula in the stomach and a cannula in the duodenum. In a few experiments there was no secretion whatsoever over a period as long as 375 minutes. Studies of pregnant dogs by McCarthy, Evans & Dragstedt (14) showed that pregnancy did not have a consistent effect in either stimulating or inhibiting gastric secretion. A profound and continued hypersecretion of gastric juice occurred during lactation. Detrick and co-workers (15) found that preirradiation of "Shay" rats subjected to pyloric ligation resulted in a great variation in the activity of pepsin and hydrochloric acid. When the activity increased, there were changes in the stomach rumen of a lytic, ulcerative nature; when activity decreased, lesions formed which were comparable to the changes occurring from irradiation alone. Irradiation alone reduced the lytic effect on the epithelium of the rumen, but the accompanying vascular effect was equally severe in normal and in Shay rats. Removal of the animal's thyroid, adrenal glands, and ovaries reduces the volume of peptic activity of gastric juice and causes an involution of the zymogenic cells comparable to that which occurs after hypophysectomy (16). These results seem to indicate that anterior hypophysectomy may regulate the zymogenic cells by way of the thyroid and adrenal cortex, with the latter gland primarily involved. Evidence is available, according to Sun and co-workers (17), to suggest that the gastric secretion can be depressed by hypothyroidism which, in turn, depresses adrenal function.

Carbonic anhydrase seems to be an essential factor in the production of hydrochloric acid (18). In human beings with duodenal ulcers and in normal persons, acetazoleamide (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide; Diamox), a potent carbonic anhydrase inhibitor, did not affect the secretory volume but exerted significant inhibitory effect on hydrochloric acid. The way chloride passes from the parietal cell into the stomach is still a moot question. A consistent difference between the relative rates at which bromide and chloride pass from the gastric mucosa seems inconsistent with the theory that halogens penetrate the mucosa by simple diffusion (19). These observations would seem to support the concept of passage in a combined state. The active transport of chloride ions, which seems quantitatively to account for the electric current produced in the isolated mucosa of a frog, is consistent with this concept of passage in a combined state. The rate of absorption of water from the stomach and small bowel of human beings (20) has been studied by accurate measurements of heavy-water absorption. In the stomach, 67 per cent of the water was absorbed in 34 min., and 95 per cent in 54 min. In contrast, the absorption of water from the small bowel was much faster, 67 per cent being absorbed in 3.7 min. and 95 per cent in 10 min. Oler & Craemer (21) found that many foods sold commercially contain emulsifiers. The effects on gastric acidity of two of these emulsifiers were tested on 12 persons by the method of fractional gastric analysis. A detectable influence of the compounds on gastric acidity was not noted.

Many studies have been made to develop and evaluate methods for

determining hydrochloric acid secretion in the stomach without the use of a gastric tube (22, 23). Quininium-resin may be given orally and if hydrochloric acid is present in the stomach it frees the quinine, which will then be absorbed and excreted in the urine. This has been found to be a useful screening test and may be quite helpful in geriatric patients. Behr & Lawrie (24) emphasized that care must be exerted to be sure the patient has not received substances containing aluminum, bismuth, barium, calcium, magnesium, kaolin, iron, or vitamins for at least two days prior to making the test. An elevated concentration of urea in the blood does not seem to interfere with the ability to secrete quinine, nor does albuminuria interfere with the test for quinine. The efficient absorption of quinine may occur with mucous gastritis and perhaps with steatorrhea. Azure A cation has been used similarly (25). The azure A is released from the compound if hydrochloric acid is present and is detected by the change of color in the urine.

Methods have been developed for determining the excretion of uropepsinogen (26). The partition of pepsinogen between the urine and the gastric juice was found to be approximately 1:99. Long-term studies of uropepsinogen may allow an evaluation of the effects of medication on secretion of pepsin. Sircus (27) made studies of 61 normal persons who had a mean average excretion of uropepsinogen of 262 μg. per 24 hr. In patients with duodenal ulcer the excretion of uropepsinogen was double that for normal persons. Uropepsinogen was not found after total gastrectomy, and only rarely was it detected after partial gastrectomy. A close correlation existed between the output of uropepsinogen and the response of the parietal cells to the triple-dose histamine test. Excretion of uropepsinogen in cases of pernicious anemia was extremely low, if any was present. Patients with carcinoma of the stomach had less uropepsinogen than normal persons, but the finding did not have diagnostic value. Lumme and co-workers (28) reported that 45 patients having pernicious anemia owing to tapeworms excreted uropepsinogen at a normal rate. Smoking, according to Bornstein & Eichen (29), increased the average secretion of uropepsinogen to a concentration 43 per cent higher than that found in nonsmokers. Excretion of uropepsin was reported by Cubberley and co-workers (30) to be low as a rule in patients with atrophic gastritis and increased in those with hypertrophic gastritis. In this way the excretion parallels the gastric acid secretion as measured by histamine stimulation. Administration of atropine reduced the output of uropepsin an average of 57 per cent in six patients. Excretion of uropepsin was usually diminished in cases of gastric carcinoma and partial gastric resection, usually normal in benign gastric ulcer with gastroenterostomy alone, and increased after the administration of corticotropin.

Gastric Ulcer

Medical treatment.—In a study reported by Nasio (31), Banthine administered orally prophylactically to dogs for 5 to 15 days failed to prevent cinchophen from causing uclers; when given intravenously, it impeded the

development of ulcers. Banthine given orally with the cinchophen inhibited the formation of gastric ulcers. In a dog with a Mann-Williamson ulcer, Sandweiss (32) found cortisone and adrenocorticotropic hormone (ACTH) to have a beneficial effect with increased postoperative survival time. Notkin (33) made a study of the effectiveness of a protein-free robaden extract prepared from the mucosa and muscularis of the stomachs and small intestines of freshly slaughtered hogs. It may be given intravenously and causes the gastric mucosa to absorb histamine-like substances and pepsin. Anti-ulcer activity is present without an anti-secretory mechanism. Patients with gastric ulcers have been treated by irradiation of the stomach and observed for as long as 17 years (34); 4.1 per cent of the observed group actually had a malignant gastric lesion and such a lesion developed later in 1.7 per cent. Complications attributable to irradiation have not been noticed. Moderate roentgen irradiation of the fundus and body of the stomach, for the purpose of decreasing completely or partially the secretion of hydrochloric acid, was felt to be a safe and valuable adjunct to the conventional treatment of benign gastric ulcer. The use of phenylbutazone was found by Christensen (35) to result in the formation of gastric or duodenal ulcers, which bleed frequently and may perforate. This drug may be dangerous, and it should be administered only after meals and with milk and alkali. It probably should not be used by patients known to have gastric or duodenal ulcers.

Surgical treatment.—The annual report of surgery of the stomach from the Mayo Clinic for 1953 by Priestley and co-workers (36) gave a mortality rate of 5.1 per cent for partial gastrectomy performed for gastric neoplasms and a mortality rate of 17.4 per cent for total gastrectomy for the same condition. Partial gastrectomy performed for the treatment of benign gastric ulcer had a mortality rate of 1.7 per cent and for duodenal ulcers a mortality rate of 1.4 per cent. Partial resection gave an excellent result in 86.5 per cent of patients who had a gastrojejunal ulcer after a gastroenterostomy, whereas vagotomy relieved only 77.8 per cent of these patients. Vagotomy relieved the symptoms of 70 per cent of patients in whom ulcers developed after a partial gastric resection. Movius, Dagradi & Weinberg (37) reported that local excision of benign gastric ulcer combined with vagotomy and an emptying procedure was tried in 74 patients and seemed reasonably satisfactory. Marginal or stomal ulcers occurred in 1.3 per cent of the cases reported by Palumbo, Mazur & Doyle (38) in whom partial gastrectomy was performed but in no patient treated by both partial gastrectomy and vagotomy.

The nutritional status of animals subjected to the Billroth II operation for subtotal gastrectomy was markedly inferior to that of animals subjected to the Billroth I operation and segmental types of subtotal gastrectomy (39). The nutritional status after the segmental type of subtotal gastrectomy was essentially normal. The nutritional status after the Billroth I operation for subtotal gastrectomy was inferior to the nutritional status after a segmental type of operation, but the differences were not great. The problem of nutrition after complete gastrectomy is a very serious one. In both ani-

mals and human beings digestion and nutrition appeared better if segments of isoperistaltic colon had been transplanted (40, 41). This procedure has been tried in human beings and seems worthy of further trial even though technically it is somewhat difficult to perform.

A macrocytic, megaloblastic anemia eventually occurs in all patients who have had total gastrectomy (42, 43). Anemia that develops shortly after operation is due to loss of blood, but later it becomes megaloblastic in type. This occurs approximately 16 months after operation. Brotmacher (44) noted electrocardiographic changes in patients who had had partial gastric resection and who drank large amounts of water; the changes were thought to be on a mechanical basis.

The dumping syndrome can be a great problem in patients who have had gastrectomy (45). Alterations in the volume of blood, resulting from intrajejunal administration of hypertonic solutions to gastrectomized patients, indicate that a shift of fluid into the intestinal tract occurs, mediated by differences in osmolarity between the administered solution and the plasma.

Massive Gastrointestinal Bleeding from the Stomach

Gunz, Gebbie & Dick (46) made repeated determinations to show the amount of blood lost in gastrointestinal hemorrhage and whether bleeding was continuing. Giving blood freely and operating early, if continued or excessive loss of blood was evident, reduced the mortality rate of 88 patients to 7.5 per cent, as compared to a mortality rate of 17.2 per cent in a group treated with less blood and later operative procedures.

Berson (47) found that changes in the blood volume may be studied by labeling the albumin and the plasma with Evans blue dye (T-1824) or with radioiodinated serum proteins. Tagged red blood cells may be used to determine the erythrocyte pool, and labeled albumin for the plasma pool. Calculations of the total volume of blood from the albumin or erythrocyte dilution alone are not likely to be in error by more than 7 per cent. Recurrent massive gastrointestinal hemorrhages may occur in patients with familial hemorrhagic telangiectasis [Hardt and co-workers (48)]. This is a rare cause of bleeding and the only specific treatment is replacement of blood. Occasionally an aneurysm will rupture into the stomach according to Millard (49). If a bleeding point cannot be found, injection of vessels may provide a diagnosis. There are only about 16 authenticated cases of ruptured aneurysm into the stomach in the literature.

In a study of a group of patients with portal cirrhosis who bled, Fainer & Halsted (50) found that 59.2 per cent bled from esophageal varices, 2.6 per cent from gastric varices, 18.4 per cent from peptic ulcer, 5.3 per cent from gastric erosion, 1.3 per cent from hiatal hernia, and 13.2 per cent from undetermined causes. Palmer (51) is of the opinion that gastrointestinal hemorrhage may occur as a complication of leukemia, but it should not be assumed that hemorrhage is always directly related to this blood disease. Of five patients with leukemia and hemorrhage, three were definitely shown

to be bleeding from a gastric or a duodenal ulcer, and all five had peptic ulcers. Hemorrhagic lesions occurred in the upper portion of the gastrointestinal tract in 34 of 480 patients with acute bulbar poliomyelitis as reported by Schaberg, Hildes & Alcock (52).

Several papers have appeared discussing benign prolapse of the gastric mucosa [Lichstein (53)]. Clinically the symptoms suggest an atypical ulcer. The roentgenogram shows a mushroomlike deformity into the duodenum. Of the patients whose cases were reported 22 per cent had gastrointestinal hemorrhage. Gastritis was present in 55 per cent of those who underwent gastroscopy. Benign prolapse of the gastric mucosa may be confused with pedunculated gastric polyps, hypertrophic gastritis, prepyloric ulcer, primary or metastatic adenocarcinoma of the stomach, antral gastritis, and diffuse gastric lesions. The symptoms can usually be relieved by medical measures. Blain & Hamburger (54) suggest, however, that in some instances surgical measures may be required. If operation is required, partial gastric resection is the treatment of choice.

Carcinoma of the Stomach

For several years carcinoma of the stomach has accounted for about 10 per cent of the total deaths from cancer. Statistics reported by Palmer (55) show that 2 to 2½ times more persons living in northern cities of the United States had carcinoma of the stomach than those living in southern cities.

The difficulties in diagnosing the small cancer have been emphasized by numerous investigators (56). If the cancer looked like a benign ulcer and was less than 1 cm. in diameter when removed, 82 per cent of the patients survived five years. Even if the cancer was as large as 4 cm. in diameter and yet appeared benign, the survival rate was 44.7 per cent.

Hirschowitz and co-workers (57) and Gasster and co-workers (58) found that defoaming agents used at the time of gastroscopy allowed a much better examination in many instances. In no case was there a contraindication to the use of these silicone anti-foaming agents.

Gastroscopy, as declared by Meadows & Lefeber (59), was indicated if the x-ray findings were indefinite or if the symptoms were not in keeping with the diagnosis. Griffin (60) found that not all lesions on the greater curvature were malignant. Templeton (61) reported that the accuracy of radiologic diagnosis of gastric carcinoma varied from 72 to 96 per cent. Spot-film roentgenography was somewhat helpful. Jennings & Richardson (62) related that giant ulcers of the lesser curvature, when above the angulus, were frequently benign. Most gastrocolic fistulas, according to Bachman (63), were in association with carcinoma of the stomach, carcinoma of the colon, or a complication of gastroenterostomy. The size of the intra-abdominal mass and the presence of a fistula were not contraindications to operative exploration in cases of neoplastic cologastric involvement.

"Pancreatospleno-total gastrectomy" was still used by a few surgeons according to Brunschwig (64). Only three patients who had undergone this

procedure were living and well without evidence of disease more than five years after operation. Mulligan & Rember (65) reported that the survival rate was extremely poor for mucous cell carcinoma, being only 2 per cent. A "second look" operation about six months after the initial operation was found helpful by Wangensteen and co-workers (66) and by Bowden, Booher & McNeer (67) in a few instances. This was not recommended for general acceptance. After an operation for benign ulcer, Freedman & Berne (68) found that gastric carcinoma seldom occurred in the gastrojejunal stoma. Only 55 such cases have been recognized, and in the average patient cancer developed 17 years after the first operation. Abdominal exploration was suggested as an indispensable prelude to vagotomy for the so-called benign gastrojejunal ulcer.

Etiologic aspects of gastric carcinoma.—Very little new or significant information has been offered regarding the etiology of gastric carcinoma. In a statistical and philosophical review by Ivy (69) it was concluded that the gastric mucosal cells had to be genetically susceptible to the induction of a malignant change. The malignant change was induced by nonspecific irritants, chronic gastritis, or specific carcinogens. Specific carcinogens, according to Ivy (70), may be a major cause of carcinoma of the stomach. Mucous secretion and mucosal cells shed superficially protected the gastric epithelium from dietary carcinogens which were not water-soluble. Water-soluble carcinogens could be absorbed into the crypts without preceding damage. In the human stomach local hyperplasia of the mucous cells should be suspected as a possible origin of carcinoma. Overheated fat (350°C). contained a low-grade carcinogen active when given intravenously to rats. Certain certified food dyes and other substances such as hot drinks or hot food may injure the gastric mucosa.

Benign Lesions of the Stomach

Hypertrophic gastritis was difficult to distinguish from malignant disease of the stomach (71). It was not thought to be necessarily a premalignant lesion. Kenney, Dockerty & Waugh (72) metioned that giant hypertrophy of the gastric mucosa was often associated with multiple adenomas of the endocrine system, and in some instances with hypoproteinemia. There was a predilection for the greater curvature. According to Ylvisaker and co-workers (73), gastroscopic and histologic findings correlate well when the gastric mucosa appears normal. Microscopic studies showed normal mucosa in patients with hypertrophic gastritis diagnosed gastroscopically. Atrophic gastritis seen gastroscopically correlated well with atrophic gastritis diagnosed histologically.

An excellent review of the entire subject of gastritis by Palmer (74) suggested that the symptomatically important form of "chronic gastritis" was often not gastritis at all but functional disease characterized by a tense stomach. It was recommended but not urged that the expression "hypertonicity of the stomach" be used rather than "chronic hypertrophic gas-

tritis." Eosinophilic infiltrations of the stomach have been described by Swarts & Young (75) and by Judd, Civin & McIlhany (76). Diagnosis of this rare condition can be made only by biopsy. Usually it was felt to be a manifestation of some systemic disease, but the possibility of malignant disease must not be excluded. Niemetz & Wharton (77) are of the opinion that benign gastric polyps should be studied by both x-ray and gastroscopic methods. In their study the symptoms were protean, and none was pathognomonic. In a study by Grimes (78) of 48 patients with gastric polyps eight were found to have malignant lesions. Gastric sarcoidosis was a rare condition but Pearce & Ehlrich (79) and Sirak (80) found that it may be confused with carcinoma of the stomach. Amyloid disease, according to Shnider & Burka (81), may involve the stomach, and it was difficult to distinguish from primary gastric carcinoma. Usually a careful search revealed other regions involved by amyloid disease.

DUODENUM

Thomas (82) reminds us that the reason for conduction of food in the intestine is still not satisfactorily explained. A tentative explanation of forward conduction based on the gradient theory plus the hypothetical pacemaker or pacemakers has been suggested. Evidence in a report by Hunt & Kay (83) seemed definite that the vagus nerve can sway the maximal secretory power of the parietal cell. There was a reduction of the mean volume of the secretion of the parietal cells in response to histamine after vagotomy. In patients with duodenal ulcer the maximal secretory capacity and the basal secretion of acid were both greater than normal, but the ratio of basal to maximal secretion was the same in both normal subjects and patients with duodenal ulcer. Thus there seemed no need to postulate any increase in excitation bearing on the parietal cells in patients with duodenal ulcer during the basal secretion. Again pain has been produced in four of seven patients with duodenal ulcers by the intraduodenal administration of 0.1 *N* hydrochloric acid at a rate that lowered the duodenal pH to 1.88 or less (84). Intraduodenal administration of the hydrochloric acid constantly inhibited motility of the gastric antrum but did not allow duodenal motility.

Although the symptoms of a patient with duodenal ulcer usually are rather characteristic, Seigle & White (85) reported that 40 per cent of 269 patients with active duodenal ulcers had some type of colonic malfunction. Of these patients 4.5 per cent had had symptoms of malfunction prior to the onset of the duodenal ulcer symptoms; 17 per cent had classic symptoms of irritable-bowel syndrome. Gross gastrointestinal bleeding was studied by Hodgson & Kennedy (86) in a group of 246 children. The duodenum was the site of bleeding in 37 per cent of the patients and all of them were more than two years of age. Obstructive jaundice as a complication of peptic ulcer may not be a rare condition in the opinion of Schneider & Hammarsten (87). Four cases were described which were encountered in one institution over a period of 18 months.

Primary diverticula of the duodenum were relatively frequent benign lesions according to Waugh & Johnson (88). Only 1 to 2 per cent of these patients had symptoms severe enough to require an operation. Only half of those operated on were benefited by their operation. Small & Berman (89) found that occasionally an annular pancreas may produce obstruction of the duodenum. Duodenojejunostomy was the operation of choice. Another very rare disease of the duodenum was cystic dilatation of Brunner's glands, a condition which simulated duodenal mucosal polyps (90). The cystic dilatation of Brunner's glands should be treated in the same manner as a duodenal ulcer. Traumatic or spontaneous intramural hematoma of the duodenum did not produce a specific symptom pattern according to Felson & Levin (91). Four cases of this extremely rare condition were demonstrated roentgenographically by an intramural mass with a coil-spring mucosal pattern. Roentgenograms in a single case of hyperplasia of the papillary lymph nodule of the duodenum reported by Golodner, Slobodkin & Ripstein (92) showed multiple "buckshot" filling defects in the duodenal bulb.

Isolated case reports and reviews of the literature collected by Weinsaft (93) indicated that carcinoma of the duodenum was noted about once in every 3,000 necropsies. The symptoms were variable and it was usually fatal within six to eight months. The five-year survival rate was 5.2 to 6 per cent. Of the cancers 66 per cent were located in the second or ampullary portion of the duodenum and 22 per cent in the supraampullary region. Everson & Cole (94) reported the case of a patient who had lived for 10 years after undergoing pancreatoduodenectomy for carcinoma of the ampulla of Vater. A review of the literature indicated that there were at least five other such cases.

Medical Treatment of Duodenal Ulcer

No very dramatic contributions have been made with regard to the medical treatment of duodenal ulcers [Sandweiss, Scheinberg & Saltzstein (95)]. Two-thirds of 43 patients who failed to become symptom-free on conventional treatment for duodenal ulcers responded favorably after the administration of uranthelone (Kutrol), but later recurrences developed in half of these. It appeared that peroral doses of Kutrol have anti-ulcer activity against the Mann-Williamson ulcer in dogs.

Lorber & Shay (96) reported the cases of 41 patients with abdominal pain due to duodenal ulcers who were treated with 25 to 37 mg. of bentyl hydrochloride three times a day and obtained relief of symptoms. In animal experiments this drug was shown to have a parasympathetic depressant effect, a direct action on the smooth muscle and a local anesthetic effect. Bentyl more often depressed than abolished the urecholine-induced activity. Belladonna alkaloids had an adverse effect in the treatment of benign pyloric obstruction according to Kramer (97). In a very small series of cases Hardin, Levy & Seager (98) found that bentyl and bellafoline were active antispasmodic drugs which caused few unpleasant side effects yet gave a large degree

of relief from symptoms. Gunn & Allen (99) found that Banthine occasionally caused paralytic ileus. In five cases hemorrhage of the upper portion of the gastrointestinal tract was treated with methantheline bromide (Banthine) and paralytic ileus developed during treatment.

Detergents such as are used occasionally in the treatment of duodenal ulcer may produce marked inhibition of the production of pancreatic amylase, lipase, and trypsin, and also may have an irritant effect on the bowel, thus decreasing intestinal digestion [Fuchs & Ingelfinger (100)]. The chance ingestion of detergents during household use does not interfere with intestinal absorption.

The effect of body position on the gastroduodenal arterial pressure was studied by Cantor and co-workers (101) by making models from cadavers. The work with models suggested that the patient in the Trendelenburg position and turned on the right side would have decreased pressure in the gastroduodenal artery. It was thought that this position might be of value in the management of penetrating hemorrhagic duodenal ulcers. This seemed to be helpful in six patients.

A group of 75 patients who had had partial gastric resection 10 years previously were studied by Wells & MacPhee (102). Only 47 were thought to be well. In some of these patients serious symptoms did not occur until many years after gastrectomy. Anderson, Gunn & Watt (103) found that gastric tuberculosis developed in 16 (3.3 per cent) of 418 patients surviving partial gastric resection. Probably the presence of active tuberculosis should be accepted as a contraindication to partial gastric resection.

The milk-alkali syndrome was discussed as a complication of the treatment of duodenal ulcer (104, 105). All patients studied had drunk large amounts of milk and had used absorbable alkali. Prior to the development of this syndrome they often complained of a distaste for milk, anorexia, nausea, vomiting, weakness, and clouding of the sensorium. The condition was distinguishable from primary hyperparathyroidsm by the absence of hypercalciuria and because of the rapidity with which the uremia and hypercalcemia disappeared when milk and antacids containing absorbable alkali were avoided.

SMALL INTESTINE

In the past year and a half several authors have emphasized a peculiar syndrome associated with carcinoid tumor of the small intestine, usually with hepatic metastasis (106, 107).[3] Cutaneous phenomena are striking and include a reddish-blue cyanosis and telangiectasia; attacks of flushing are associated with cyanosis which deepens to a very dark purplish red. As will be recalled, Waldenström earlier emphasized this cutaneous phenomenon as an important diagnostic sign of carcinoid tumor of the small intestine. Pathologically,

[3] See also Thorson, A., *et al.*, *Am. Heart J.*, **47**, 795–817 (1954); Bean, W. B.' Olch, D., and Weinberg, H. B., *Circulation*, **12**, 1–6 (1955); and Spain, D. M., *Am. J' Med.*, **19**, 366–9 (1955).—Ed.

the cusps of the pulmonary valve are partially fused. The dark reddish-blue cyanosis seems attributable to pulmonic stenosis and has been previously noted. Periodic flushing is more difficult to explain. An indole derivative, enteramine (5-hydroxytryptamine; serotonin) has been found in argentaffin tumors and may be the responsible substance. Clinically, the attacks of flushing are often associated with dyspnea and bouts of diarrhea. In animals, the indole derivative increases intestinal peristalsis, constricts the bronchi, and raises the pulmonary arterial pressure; injected intradermally it produces local congestion. This may explain the dyspnea and diarrhea often seen. It is possible that prolonged secretion of the enteramine with its vasoconstrictor action on the lungs and bronchi may have some role in the pathogenesis of the pulmonic valvular stenosis.

It is suggested that the finding of increased urinary excretion of 5-hydroxyindole acetic acid, the product of oxidative deaminization of serotonin, might be increased in patients with malignant carcinoid, and that a method for assay might serve as a test in diagnosing malignant carcinoid (108).

The epithelium of the small intestine acts, in many ways, like the renal tubules. Blickenstaff (109) reported that subcutaneous injection of pitressin produces an increase in the absorption of water from isosmotic saline. In dogs with upper jejunal fistulas this same author (110) found that absorption of 0.9 per cent solution of sodium chloride was decreased by addition of Mercuhydrin or mercuric chloride solution. The cases of 35 patients have been reported in whom an isolated segment of ileum was used as a urinary channel instead of an ureterocolic anastomosis. None has had an attack of clinically recognizable renal infection and only one has had transient acidosis. There has been occasional hyperchloremia but concentrations of urea in the blood have remained normal. Preservation of the renal substance, as judged by excretory urography, seems better than ureterocolic anastomosis in the opinion of Annis, Hunter & Wells (111). The intravenous glucose tolerance test is considered different from the oral test chiefly in its bypassing of intestinal absorption. Recent studies by Scow & Cornfield (112) suggest that, in addition, the oral glucose tolerance test reflects hepatic utilization to a much greater extent than does the intravenous test. The papers of Engel & Jaeger (113) and of Pareira and co-workers (114) are representative of the problems associated with nasogastric tube feeding. Dehydration with hypernatremia, hyperchloremia, and azotemia are noted with feedings containing much protein without adequate fluids to allow for the excretion of the nitrogen and other solutes from the diet and from tissue catabolism. Five of 16 persons in otherwise excellent health failed to show any appreciable elevation of the serum concentration of vitamin A during an eight-hour period after administration of the test dose. After eating, the serum samples showed an immediate increase in concentration of vitamin A. It is suggested by Mendeloff (115) that the lacteals may be activated in some way by eating so as to expel the vitamin A which they contain into the blood stream. Three cases of idiopathic steatorrhea and a doubtful fourth case are described by

Paulley (116) in which material for biopsy was taken at laparotomy. All showed chronic inflammation of the jejunum and lymph nodes. Photomicrographs of the jejunum of two of these were presented with control sections taken at the time of operation for partial gastrectomy with significant differences readily apparent. Hornsby & Baylin (117) suggested in their study that roentgenograms of the small bowel may aid in differentiating sprue from pancreatogenous steatorrhea. Dilated gas-filled loops of small bowel simulating paralytic ileus, Kantor's moulage sign, and coarse mucosal folds were much commoner in the group of patients having sprue. Further information has been reported by Lewis & Partin (118) concerning fecal fat on an essentially fat-free diet. In one study specimens of stool were obtained every 24 hr. from three adults, over a two-month period. The otherwise adequate diet contained less than 25 mg. of fatty acid daily but the daily excretion of lipid was about 2 gm., a finding consistent with the belief that there is excretion by the intestinal mucosa. This is one of the few reports on fecal excretion on such a diet. Studies of rabbits and rats by Friedman (119) support the conclusion that the presence of feces within an intestinal loop is an important causative factor of ulceration and strictures after irradiation. With deviation of the fecal stream by means of colostomy, doses of radiation sufficient to produce intestinal ulcers failed to result in ulceration. Perhaps, in human beings, the use of antibiotics to alter the intestinal flora likewise might protect against actinic enteritis. Addison's disease is known to be associated with frequent disturbances in gastrointestinal function. In investigating the explanation of this in intact rats it was found by Streeten, Hirschowitz & Henley (120) that extracts of adrenal cortex significantly increased motility. Larger doses of cortisone inhibited gastrointestinal motility and produced a negative potassium balance. Administration of supplementary potassium protected the animals from the inhibitory effects of cortisone on motility. The stimulant properties appear to depend on the predominantly salt-retaining steroids, probably corticosterone and possibly aldosterone (electrocortin).

LARGE INTESTINE

Examples of the occurrence of pseudomembranous enterocolitis after antibiotic therapy continue to appear in the literature (121). Cultures usually showed the presence of *Micrococcus pyogenes*. The course was fulminating and the patient frequently died within 36 hr. of the onset of the disease. Wilson & Qualheim (122) reported on a form of acute hemorrhagic enterocolitis afflicting chronically ill patients; it simulated the typical pseudomembranous enterocolitis, but intestinal hemorrhage was commoner and fever and peritonitis less frequent. Hemorrhagic enterocolitis involved chiefly the distal half of the small intestine and the proximal half of the colon. Neter & Walker (123) found that a polyvalent enteric hemagglutination test employing antigens of *Salmonella*, *Shigella* and *Escherichia* may serve as a useful screening aid. Two grams of bacitracin and 3 gm. of neo-

mycin given daily for three days showed little absorption, yet these drugs seemed to sterilize the bowel adequately according to Fog (124). Sheep suffer from a condition called "enterotoxemia." *Clostridium welchii* epsilon toxin produced by *Cl. welchii* type D caused death in these sheep [Gleeson-White & Bullen (125)]. This organism occurred normally in the human bowel, but in a patient it became a pathogen when intestinal obstruction intervened.

A synergistic amebicidal effect of tetracycline, oxytetracycline (Terramycin) and carbomycin on cultures of *Endamoeba histolytica* was described by Seneca & Bergendahl (126). Dwork (127) related that endamoebae depend for survival on the availability of mechanisms, perhaps enzyme systems, outside themselves and they will not grow *in vitro* without bacteria or trypanosomes being present. It may be that the effect of chlortetracycline (Aureomycin) and oxytetracycline, which act as amebicides, is due to the disturbance of one of these systems. Fumagillin, as reported by Barrios (128), seemed to be an effective amebicide in concentrations of 1:8,000,000 but did not affect the bacterial flora. The side effects were minimal. White (129) used piperazine hydrate in the treatment of ascariasis. A report from Moscow by Talyzin (130) suggested that oxygen be introduced through a duodenal tube until uniform tympanites is produced. This supposedly killed the ascarides. Manson's schistosomiasis is becoming a greater problem than heretofore in the United States with our increasing Puerto Rican population. Latty and co-workers (131) recommend that stools of patients suspected of having this disease be examined for the eggs and that rectal biopsy be performed.

The question has arisen as to how far the proctoscopist can see up the rectum with a 10-inch sigmoidoscope. By attaching silver clips to the mucosa at the extreme reach of the 10-inch sigmoidoscope in 50 patients, Shatz & Freitas (132) found that they could see as far as the proximal portion of the distal bend of the sigmoid. The motility of the sigmoid colon in the intact human being was observed by Rosenblum & Cummins (133) to be greatly reduced during naturally occurring drowsiness and sleep. Oral or intravenous administration of amobarbital sodium (sodium amytal) produced colonic hypomotility during periods of induced drowsiness or sleep.

Cross (134) reported that increased atmospheric pressure and the inhalation of 95 per cent oxygen and helium-oxygen mixtures affected the viability of the intestinal wall and the absorption of gas in closed-loop obstructions. The use of 95 per cent oxygen at 2 atmospheres of pressure for 6 hr. resulted in absorption of 44.8 per cent of the injected air. The viability of the bowel in the closed-loop obstruction was well preserved for periods up to 92 hr.

In a series of 111 patients with diverticulitis Hoar & Bernhard (135) found 37 per cent to have rectal bleeding and yet no associated carcinoma of the colon. In a group of 236 patients with diverticulosis 16 per cent had rectal bleeding. Nevertheless, it was emphasized that massive colonic hemorrhage with diverticular disease was an indication for surgical intervention. Young

& Howorth (136) often found it difficult to distinguish a diverticulum from a polyp of the colon by roentgenograms alone. Polyposis of the colon and rectum seemed to have a definite inherited tendency according to studies by Woolf, Richards & Gardner (137) and by Brasher (138). Routine sigmoidoscopic examinations carried out in various clinics throughout the United States have shown that approximately 5 per cent of all adults have polyps of the rectum or sigmoid. The frequency among relatives was much greater. The treatment of choice for polyposis, in the opinion of Everson & Allen (139), seemed to be removal of all of the colon except the rectal segment. This segment should be carefully observed and treated through the proctoscope. Periodic examinations of the retained colon must be made during the remainder of the patient's life. Rosenberg (140) related that a wheal formed by introducing saline solution into the submucosa beneath the sigmoidal or rectal polyp prior to electrocoagulation or fulguration of the lesion may afford protection against too great a thermal injury to the intestinal wall. Diverticula of the ileocecal region were rare, but occasionally Ferguson (141) found that such a diverticulum perforated and formed a granulomatous mass. Treatment of this condition was surgical removal of the mass. A normal or hypertrophied ileocecal value may prolapse into the cecum and produce a translucent shadow (142, 143). This shadow may simulate a polypoid lesion of the cecum. Insufficient evidence was avilable to determine whether this constituted a definite syndrome. Denenholz & Feher (144) reported that intussusception can often be reduced if barium is permitted, with great caution, to enter the rectum and distal portion of the colon. In most carefully studied cases of congenital megacolon, according to Keefer & Mokrohisky (145), ganglion cells were absent in the involved region. In some instances there were two narrowed portions and in rare instances the aganglionic segment involved the entire colon.

An excellent review of chronic ulcerative colitis by Zetzel (146) suggested that psychiatric disturbances were important. The treatment of ulcerative colitis was primarily medical, but total colectomy was the only method of cure. Malignant lesions occurred about four times more frequently among psychiatric patients than in the general population and were often fulminating in character. Ileostomy alone was not a very satisfactory treatment of chronic ulcerative colitis in the opinion of Rogers, Bargen & Black (147). A study was made of 124 patients; 73 per cent required further surgical treatment. In 41 per cent of the patients, symptoms of active colitis continued after the stoma was made. Only 14 per cent of the patients who survived operation for one year failed to have some complication resulting from or associated with their ileostomy. Ileostomy and colectomy represented the only effective surgical treatment for patients with severe diffuse ulcerative colitis (148). Complete rehabilitation of these patients was dependent on a properly constructed ileac stoma. Dennis & Karlson (149) studied 276 cases of idiopathic ulcerative colitis either of advanced or very active character. Of the 276 patients who were treated conservatively or who had undergone

surgical procedures as an acute emergency, only 29 per cent were found to be living. Only 27 per cent of these survivors were free of symptoms. The rate of risk of primary colectomy at the time of ileostomy was between 2 and 5 per cent, but this was only a fraction of the mortality rate accompanying ileostomy alone. Patients with chronic ulcerative colitis, according to MacFadyen and co-workers (150), showed a marked tendency toward reduced concentrations of serum sodium with marked retention of calcium and perhaps retention of phosphorus both before and after operation. An intestinal excretion of anions occurred over and above that of chloride, bicarbonate and phosphate.

A study of 200 consecutive cases of chronic ulcerative colitis by Jackman (151) showed that 16 per cent of the patients had anorectal complications. Polyps or pseudopolyps occurred in 11 per cent. Lower rectal strictures occurred but were seldom an indication for ileostomy. Recurrent abscesses and, finally, anal incontinence from fibrosis often occurred. About 11 per cent of the total number of patients having chronic ulcerative colitis were children between the ages of 1 and 15 years (152). Although the physician's approach to the disease in a child was different from that in an adult, the complications in both were the same. At necropsy Parker & Kendall (153) found only 3.3 per cent of 73 patients with chronic ulcerative colitis to have cirrhosis, and 24 per cent had severe fatty changes of the liver. This was at variance with the report by Kleckner and Bargen, who, in needle-biopsy specimens, found cirrhosis in 18.7 per cent.

Corticotropin and cortisone were used by Kirsner & Palmer (154) in the treatment of 120 patients with chronic ulcerative colitis. These hormones were not a specific cure but were a useful therapeutic adjunct. Compound F seemed more effective than cortisone but less effective than corticotropin (ACTH). Intravenous administration of trypsin was tried by Milanés, Piedra & Morales (155) in the treatment of a small group of patients with chronic ulcerative colitis. In almost every case marked side effects developed.

A review made by Felson & Wolarksy (156) of 1,204 cases of chronic ulcerative colitis and ileitis showed 3.1 per cent to occur in 21 family groups. These diseases tended to follow acute bacillary dysentery. Regional (segmental) colitis constituted about 4 to 10 per cent of all cases of chronic ulcerative colitis (157, 158). The right side of the colon was more frequently involved than the left, but the lesion was confined to the left side in 12 per cent. The flexures of the colon, particularly the hepatic and the sigmoidal flexures, seemed to constitute a barrier or at least a point of delay for further progression of the disease. Medical management was disappointing. Proctosigmoidoscopic examination revealed perirectal and perianal complications in 13.4 per cent. Malignant change was not encountered. The earliest pathologic lesion of regional (segmental) colitis was a purulent cryptitis, followed subsequently by formation of microscopic abscesses and ulceration of the overlying mucosa.

Carcinoma of the Large Bowel

Statistics from the Connecticut Tumor Registry, reviewed by Ottenheimer & Oughterson (159), indicated that 16.4 per cent of all cancers were of the colon and rectum. From their statistics the patient with carcinoma of the large bowel who was most suitable for treatment had been a woman 75 years of age who was a private patient and who had a localized malignant lesion of grade 1 in the ascending colon. In New Haven Cohart & Muller (160) found the relative incidence of carcinoma of the stomach was lowest in well-to-do women, while the relative incidence of carcinoma of the colon was highest in this socio-economic group. Diverticulitis and carcinoma of the colon were difficult to differentiate (161). Abdominal pain occurred in 74 per cent of the patients with diverticulitis and in only 26 per cent of patients with carcinoma. Rectal bleeding, on the other hand, occurred in 64 per cent of patients with carcinoma and in only 22 per cent of those with diverticulitis. X-ray findings indicated definite diverticulitis in about 58 per cent of the cases. The experience of Judd & DeTar (162) was that squamous cell epithelioma of the anus without inguinal node involvement was treated best by early radical surgical excision. Prostatic annular constricting lesions of the rectum were difficult to differentiate from adenocarcinoma of the rectum in the opinion of Baum & McClellan (163). In some instances a therapeutic trial of stilbesterol was in order. The "second look" operation has been further evaluated by Boeck, Bailey, Halsted & Wangensteen (164). It was not recommended for all patients, although in certain instances it seemed valuable. Damage to the rectum by radium treatment for carcinoma of the cervix occurred in about 2.4 per cent of the cases according to Strickland (165). The commonest symptoms consisted of increasing diarrhea with passage of abundant mucus and small quantities of frank blood. Tenesmus occurred, but usually this was not a dominant symptom. The patient usually looked quite well in spite of a markedly inflamed rectum.

LIVER

Adrenocortical Hormones in Hepatic Disease

Corticotropin (ACTH), cortisone, and hydrocortisone were found ineffective in influencing the course of hepatic coma in cases of advanced portal cirrhosis (166). The absence of a sense of well-being or increase in appetite expected in patients with nonhepatic disease on the dosage used was disconcerting. The recent finding that the removal of hydrocortisone from plasma is decreased in patients with severe hepatic disease has led to the postulation that the concentration of corticoids in the hepatic cells may not be increased even though the concentration of corticoids in the serum is elevated. A further study by Johnson & Bennett (167) of 54 patients with viral hepatitis demonstrated the ineffectiveness of corticotropin (ACTH) in the routine treatment. Serious complications were encountered in two

patients. In a patient with primary biliary cirrhosis, administration of adrenocorticosteroids produced a striking reduction in the concentration of alkaline phosphatase and lipides in the serum, with return to previous concentrations after withdrawal of the hormone [Carman & Giansiracusa (168)]. Diengott & Ungar (169) found that in rats cortisone exerts a deleterious effect on the liver during carbon tetrachloride poisoning and enhances fibrosis of the liver. This is in contrast to previous reports. Of interest is the observation of Patterson and co-workers (170) that cortisone causes both hydrocholeretic and choleretic activity that persists several hours after administration of the hormone. It also causes increased activity of the pancreatic enzymes of duodenal fluid. The choleretic action might explain transient decreases in concentrations of serum bilirubin during treatment of jaundiced patients with cortisone. It is suggested that pancreozymic-like action might improve the absorption of fat in patients with idiopathic steatorrhea. Other investigators, at least, have not demonstrated any deficiency of pancreatic secretions in the patient with idiopathic steatorrhea. The disappearance rate of 17-hydroxycorticosteroids and tetrahydrocortisone in the plasma has been measured by Brown and co-workers (171). Tetrahydrocortisone was uninfluenced by hepatic disease, whereas 17-hydroxycorticosteroids were inversely proportional to the degree of damage to the liver. The increase in the concentration of 17-hydroxycorticosteroids in the plasma in response to stimulation by corticotropin was normal in patients with hepatic disease even though urinary excretion was decreased. Normal concentrations of 17-hydroxycortocoids in the plasma collected at 8 A.M. suggested that a homeostatic mechanism suppresses adrenocortical secretion in patients with hepatic disease in whom the rate of removal of 17-hydroxycorticosteroids from the plasma is impaired.

Circulation

Portal hypertension.—Certain observations cast suspicion on the usual view that portal hypertension has much to do with hemorrhage from varices, according to Taylor (172). It was found that the aggregate pressure differential across the diaphragm was about 160 cm. of water when the negative intrathoracic pressure was subtracted from the positive intraabdominal pressure during inspiration. This pressure influence operates even in the normal person in whom varices do not develop. Furthermore, this tremendous pressure is greatly in excess of the pressure levels of 30 or 40 cm. considered suggestive of portal hypertension. This may explain the localization of varices and hemorrhage in this region. In support of the contention that pressure, per se, is relatively unimportant, Morton & Whelan (173) describe a patient who had had three episodes of severe gastrointestinal hemorrhage with esophageal varices but who, at the time of operation, did not have portal hypertension. Studies in the dog by Caldwell and co-workers (174) have shown that any decreases in pressure in the portal veins after ligation of the hepatic artery may be transient.

Other vascular problems.—Further data suggest a relation between the hepatic blood flow and the disappearance from the blood of colloidal radioactive gold in human beings [Vetter and co-workers (175)]. Calculations are based on the assumption that the phagocytes of the liver and spleen remove colloidal particulate matter from the blood stream. It was found that an external counter could be placed between the calves of the legs to measure the rate of disappearance. It is thought that the clearance of colloidal material is less dependent on function of the liver than is the clearance of bromsulphalein. No correlation was found between the two methods of estimating hepatic blood flow. With the use of the older bromsulphalein technic, Mendeloff (176) has found intravenous infusion of ethyl alcohol to cause a significant increase in estimated hepatic blood flow, an effect ascribed to a lowering of the peripheral resistance of the splanchnic bed. Interestingly, the fatty infiltration of the liver in alcoholic patients does not seem to alter hepatic blood flow [Kessler and co-workers (177)]. An increased difference in the oxygen saturation of hepatic arterio-venous blood was found before treatment. This returned to normal after treatment. Several authors have attempted to correlate further the pressure of the wedged hepatic vein with that of the portal vein in human beings with and without hepatic disease. By this technic it is contended by Cohn, Ordway & Ellis (178) that either portacaval anastomosis or ligation of the hepatic artery will reduce portal pressure only temporarily. The mean pressure in the hepatic vein in the occluded and the free positions in six patients without hepatic disease was, respectively, 6.8 and 4.3 mm. of mercury, a mean pressure difference of 2.5 mm. In six cases of portal cirrhosis with splenomegaly the corresponding values were: 21.7, 6.3 and 15.3 mm.; in six other cases of cirrhosis without splenomegaly and on the whole less advanced, the pressures were 12.8, 5.8 and 7.0 mm. of mercury (179). Previous studies by one group had shown that Laennec's cirrhosis was associated with a high cardiac output at rest and lowered peripheral vascular resistance, but no evidence of heart failure. Recently the same studies in patients with acute infectious hepatitis were carried out, but no such changes were found by Abelmann, Kowalski & McNeely (180). Percutaneous splenic puncture for portal venography must not be undertaken lightly. With splenic puncture for venography at the time of laparotomy in five patients with portal hypertension it was observed by Du Boulay & Green (181) that there was hemorrhage of 50 to 200 cc. of blood from the puncture wound.

In another group of 25 patients who underwent percutaneous splenoportography, splenic hemorrhage occurred in about 1 per cent; it was considered to be reasonably safe and of considerable value in preoperative localization of the site of portal obstruction according to Figley and coworkers (182). The suggestion is made that in the future this technic may have a place in the search for otherwise undetected hepatic metastasis. Tests of liver function immediately after, and one year after, operations for portal hypertension were done in patients with hepatic disease (183). Di-

version of the portal blood stream does not seem to be followed by more deterioration of liver function than is seen after other operations of comparable severity in patients with cirrhosis. It has been shown earlier that regenerative nodules in cirrhosis are vascularized by arterial blood and this may explain the ability of the patient to withstand deviation of portal blood.

An additional technic has been proposed to demonstrate the patency of a portacaval shunt. Bile acids are given by duodenal intubation (184). With closure of the portacaval shunt there is no increase in systemic bile acids.

From an experienced endoscopist comes the report by Palmer & Brick (185) that esophageal varices are commoner than suspected in noncirrhotic patients. Varices were found in four of seven patients with chronic heart failure, eight of 14 with active viral hepatitis, one of two with hemolytic icterus, one of two with amebic hepatitis, and in eight of 24 with simple portal fibrosis. In dogs, the mortality after ligation of the hepatic arterial supply seemed largely related to the fostering of necrosis of the liver by infection with intestinal bacteria. In neomycin-treated dogs the mortality was 28 per cent; in control dogs it was 90 per cent. Schatten's study (186) is one of the first in which a poorly absorbed antibiotic is used and the results suggest the efficacy of sterilization of the intestinal tract prior to excision of the arterial supply.

Pathologic States

Hepatitis.—A study of three different types of ultraviolet irradiators revealed that sterilization can be obtained only at an energy level producing extensive changes in the plasma proteins. Interestingly, in cases of hepatitis resulting from irradiated plasma the incubation periods were longer and the illness was milder than usual (187). In an attempt to eliminate asymptomatic carriers of the virus of infectious hepatitis as blood donors, tests for hepatic function were administered to 3,655 ostensibly healthy donors. The single test that most commonly showed abnormal results was the thymol turbidity test; results of this test were positive in 6.6 per cent of the cases and equivocal in 9.1 per cent. When all of the tests used were considered and an arbitrary point scoring system was employed, it was found that 30 per cent of the donors were abnormal. It is known that the results of tests for hepatic function of all proved carriers are not always abnormal (188). Fifteen patients who survived pregnancy and infectious hepatitis were studied by Frucht & Metcalfe (189). The results of the study of this small series suggest that infectious hepatitis occurring in the last trimester of pregnancy carries a high rate of mortality and a greater tendency toward the development of chronic disease of the liver than when it occurs in nonpregnant patients.

Hemochromatosis.—Clinical features and methods of diagnosis have been reviewed with respect to 27 patients seen by Stauffer, Butt & Dockerty (190). The need for a high index of suspicion is emphasized, particularly because diabetes mellitus was absent in 12 of the 27 patients. In seven, biopsy of the liver gave positive results, although biopsy of the skin gave

negative results. An eventual incidence of hepatomas in 20 per cent of the cases is cited. The classification as primary, secondary, or exogenous hemochromatosis or hemosiderosis is of interest. The secondary group included patients with refractory anemias who had received too few transufusions to account for the amount of iron found. Bothwell and co-workers (191) explained the poor prognosis of hemochromatosis in young patients by the rather high turnover rate revealed by radioiron studies. They found that even though a negative iron-balance might be maintained by phlebotomies, only about 75 per cent of the tagged iron in the plasma was being utilized for formation of hemoglobin; the remainder presumably was being deposited in various body stores. Even though the percentage of erythrocytic utilization of an injected dose of radioiron was low in the patient having hemochromatosis, this utilization could be raised after phelebotomy. In one patient with hemochromatosis treated by removal of 40 liters of blood over a period of 28 months, a substantial clinical improvement was manifested by decreased pigmentation of the skin, return of libido, and apparent amelioration of diabetes. Biopsy of the liver revealed a decrease in the amount of iron therein, even though the fibrosis remained unchanged. The high concentration of iron in the serum and the total saturation of iron-binding beta-globulin returned to normal values. It was found difficult to provoke anemia, and this suggested the ready availability of stores of iron in the tissues for the production of hemoglobin (192). On the other hand, Davey, Foxell & Kemp (193) reported the case of a patient who underwent phlebotomy to the extent of 55 pints of blood in two years and at the end of this time very severe anemia developed. Some subjective and objective improvement was felt to have taken place in spite of the anemia.

Hepatolenticular degeneration (*Wilson's disease*).— In keeping with earlier studies of the metabolic defect in hepatolenticular degeneration, it was found that after intravenous and oral administration of Cu^{64} to patients having this disease there was no secondary rise in serum radioactivity as is observed in normal persons. This secondary rise in the normal person is due to incorporation of the copper into ceruloplasmin. This protein is deficient in the patient with hepatolenticular degeneration. On the other hand, the radioactivity associated with the serum albumin after administration of Cu^{64} was found to be increased and to persist much longer. According to Bearn & Kunkel (194), this seems to be be an important factor in the pathogenesis of the disease.

As an index of the success of a treatment program for this trying disease, the excretion of copper in the urine has been measured by Cartwright and coworkers (195). When BAL was given simultaneously with casein hydrolysate, the greatest increase of copper in the urine occurred, the mean increase being 501 per cent. Seven patients who had far-advanced hepatolenticular degeneration were studied. The following abnormalities were demonstrated and summarize well the current knowledge regarding this problem: (*a*) a decrease in the total concentration of copper in the plasma, (*b*) an increase in the di-

rect-reacting fraction of copper in the plasma, (*c*) a decrease in the indirect-reacting fraction (ceruloplasmin) of copper in the plasma, (*d*) an increase in the concentration of copper in the spinal fluid, all direct reacting, (*e*) a large increase in the concentration of copper in all of the tissues studied, except cardiac muscle, skeletal muscle, lungs and erythrocytes, (*f*) a state of positive copper balance, and (*g*) an increased excretion of copper in the urine. Aminoaciduria certainly is not the only renal defect in hepatolenticular degeneration. In two siblings with this condition, Bishop, Zimdahl & Talbott (196) found the concentration of urates in the serum to be unusually low. Isotopic uric acid was used and the pool size and turnover rate were measured; the former was found to be below normal and the latter about twice normal. This is consistent with inhibition of tubular reabsorption of uric acid.

Biochemical and Physiologic Problems

Coma.—In an excellent review by McDermott, Adams & Riddell (197) on ammonia metabolism in human beings, it was again pointed out that isolated determinations of ammonia in the blood are valueless, because although the onset of hepatic coma is correlated with the elevation of ammonia in the blood, coma may sometimes persist after concentrations of ammonia have decreased. The liver is unique in its role of protecting the organism against high concentrations of ammonia in the portal vein, since ammonia is not excreted from the blood by the kidney. A more recent study of "meat intoxication" in the dog by Riddell, Kopple & McDermott (198) showed symptoms invariably associated with elevated concentrations of ammonia in the blood. Reproduction of findings by intravenous administration of urease further implicated ammonia as an etiologic factor.

More important, the brain has been found to take up ammonia when the arterial concentration is greater than 1 gamma per milliliter (199). Glutamine synthesis probably does not account for the high uptake of ammonia. On the other hand the synthesis of glutamate by the addition of ammonia to alpha ketoglutarate could account for the ammonia consumption. The ketoglutarate thereby would be removed from the Krebs' cycle and would diminish formation of other members of the cycle with reduction in oxidative phosphorylation in the brain. Reported elevations of alpha ketoglutarate in the blood during coma do not seem compatible with the theory, but this dibasic acid is not taken up by the brain and a lack of this compound could exist behind the "blood barrier." This acid could be a therapeutic agent and further investigation of it may be warranted.

"Ammonia intoxication" is seen after portacaval anastomosis and reports of this continue to appear (200 to 203). The electroencephalogram seems to be a sensitive guide in predicting mental changes. In one patient the most abnormal record noted preceded mental confusion by 12 hr. The appropriate designation "portal-systemic encephalopathy" has been coined by Sherlock and co-workers (201). Two mechanisms may be responsible for such symptoms. In one group damage to the liver is minimal, but

portal-systemic anastomoses demonstrated by portal venography are extensive. In these patients specimens obtained by catheterization of the hepatic vein reveal lower concentrations of ammonia in the hepatic vein than in the peripheral vein. With severe hepatocellular damage the concentrations of ammonia in the hepatic vein exceed those in the peripheral veins. In two patients with thrombosed portal veins but good liver function, symptoms could not be precipitated by exciting agents. In 51 patients with hepatic disease the oral administration of 3 gm. of ammonium chloride precipitated abnormally elevated concentrations of ammonia in the blood of the peripheral veins; five patients showed abnormal neurologic symptoms according to White and co-workers (204). In the dog, however, Mann and co-workers (205) have found that hepatic damage does not seem to be responsible for elevation of blood ammonia. In direct observations on the removal of ammonia by the livers of normal dogs, those having Eck fistulas, and those having ligated portal veins, it was noted that all three preparations were equally effective under maximal loads of infused ammonia. Elevations of ammonia in the peripheral blood were noted only when the portal circulation was diverted from the liver by Eck fistula, by ligation of the portal vein, or by cirrhosis of the liver.

Ascites.—Obstruction either of the extrahepatic or of the intrahepatic veins has been implicated as the cause of ascites according to Madden *et al.* (206). With irreversible ascites the obstruction is presumably due to an obliterative fibrosis of the intrahepatic systemic venous bed. Reversible ascites seems attributable to more temporary intrahepatic cellular edema with venous obstruction. In the treatment of irreversible ascites it is felt that the performance of extrahepatic portacaval shunts, ligation of the hepatic artery, or establishment of an arteriovenous fistula between the hepatic artery and the portal vein are contraindicated. Of the cadaver specimens of normal human beings that were studied 50 per cent were considered to demonstrate naturally occurring portacaval shunts of significance. A more logical treatment for refractory ascites is considered to be the production of an artificial bridge between the portal and systemic veins by the application of magnesium trisilicate to abraded areas over the superior surface of the liver and inferior surface of the diaphragm. This was carried out in two patients. Paper electrophoresis of serum proteins is considered by Kay (207) to have diagnostic value in determining the nature of ascites. In chronic hepatic disease with ascites there was a variable increase in serum gamma globulin accompanied by low or low-normal concentrations of alpha globulin. In malignant disease low, normal, or at best slightly increased concentrations of gamma globulin are overshadowed by a well-marked alpha globulinemia. Thirty-eight cases of ascites were studied.

Metabolism.—Anemia associated with disease of the liver may, on occasion, represent more than increased volume of plasma or increased hemolysis, according to Jandl (208). In cases of chronic hepatic disease, a value for hemoglobin of less than 5 gm. per 100 cc. of blood or a mean corpuscular vol-

ume of more than 130 μ^3 should alert the examining physician to the possibility of superimposed deficiency of folic acid. On diets lacking in known hemopoietic factors, alcoholic persons having chronic hepatic disease stopped drinking and exhibited an increase in the concentration of reticulocytes. With the use of a radioactive sodium-chromate method eight patients with cirrhosis were found to have increased hemolysis, a result which is well known. Gallstones were sought and found in five of these eight cases. Weinstein, Ettinger & Jones (209) reported that this increased incidence of gallstones is not so well known. Serum citrate was measured in 130 patients during the transfusion of large volumes of citrated blood. Elevations in the concentration of citrate in the serum were frequently sufficient to depress ionized calcium seriously, especially in patients with disease of the liver. A solution of calcium salts, intravenously administered, was not a satisfactory treatment and the risk of calcium overdosage was significant. Bunker and associates (210) suggested that resuspended red cells be used or that decalcified blood be prepared by collection through passage across a cation exchange resin. These authors comment on the difficulty of distinguishing the hypotension of blood loss from the hypotension secondary to a low concentration of ionized calcium in the serum. Some have suggested advantages in the parenteral use of invert sugar in the treatment of hepatic disease. Beal & Smith (211) found that a low renal threshold for fructose, however, may be associated with a greater excretion of both it and associated electrolytes. The conversion of fructose to its utilized form as glucose occurs under aerobic conditions only. This is pertinent because the liver appears to be the organ principally involved in metabolism of fructose.

Another group of investigators (212) has found that infusions of fructose and invert sugar led to smaller losses of sugar in the urine than those that followed infusions of glucose alone, both in the normal person and in the patient with hepatic disease. All of these studies suggest the need for longer periods of study by balance technics.

Amino-acid metabolism was investigated in 19 children with infectious hepatitis. A third of the patients had moderate amino-aciduria, another third had borderline amino-aciduria, and the remaining third had normal excretion of amino acids. The concentration of alpha amino nitrogen in the plasma was high in all the patients having moderate amino-aciduria and in some of those with borderline amino-aciduria. Results indicate that an actual shortage of amino acids did not exist, but only an inability of the liver to deaminate them (213). Somewhat contradictory findings were noted by Mellinkoff, Jenden & Frankland (214) when changes in the concentration of amino acid in the serum of 22 controls and 16 patients with viral hepatitis followed consumption of a standard meal containing 20 gm. of protein. In patients with hepatitis the curve for amino acid reached a lower peak more quickly and descended more rapidly than the curve for normal persons. After their hepatitis had subsided, five patients were retested and the curves were then normal. The urinary excretion of amino acid was no higher in the pa-

tients with hepatitis than in controls. London (215), an experienced worker, has reviewed the problem of metabolism of hemoglobin and of bile pigment. Quantitative differences between direct and indirect reacting bilirubin are summarized. It is re-emphasized that in normal human beings at least 10 to 25 per cent of the total bile pigment is derived from one or more sources other than the hemoglobin of mature, circulating erythrocytes. In a more recent work Najjar (216) has described the separation of the two forms of bilirubin by electrophoresis at controlled pH levels. Evidence is presented to show that once bilirubin becomes direct, after its excretion into the bile ducts, it is present in the form of a metal chelate complex that becomes stabilized by binding to protein through the metal of the complex. He has reported the conversion of direct bilirubin into indirect bilirubin by treatment of the serum with versene followed by prolonged dialysis to remove the versene. The concentration of ketones in the blood of patients having cirrhosis of the liver was found to be lower than normal in response to the stress of a standard 18-hr. fast. In these cirrhotic patients intravenous administration of glucose was less effective in correcting ketonemia than it was in normal persons. Interestingly, in the experience of Recant (217), infusions of fructose diminished the ketonemia in the group of patients having hepatic disease more strikingly than did glucose. The concentration of histamine in the blood of cirrhotic patients and of patients with jaundice caused by biliary obstruction was higher than in a group of healthy persons. A relationship was noted by Mitchell, Butt & Code (218) between the degree of pruritis and the concentration of histamine in the blood. The administration of cortisone caused a decisive decrease in the concentration of histamine in the blood, but one such patient with jaundice and severe pruritis was not relieved of the itching. An interesting finding was that methyltestosterone produced prompt relief of the itching without change in the concentration of histamine in the blood. Patients with fatty liver and other hepatic disorders seemed able to absorb and utilize large amounts of fat according to Mindrum (219). On a high caloric diet containing 300 gm. of fat, the patients with fatty livers manifested clinical improvement, regression in size of the liver, and improvement in function of the liver with disappearance, on serial biopsy, of hepatic fat. Christian (220) indicated that a high concentration of iron in the serum, that is, in excess of 300 μg. per 100 ml., is highly suggestive of viral hepatitis. Such levels are seldom attained before the third week of the disease. This high level is thought to be extremely useful in distinguishing between viral hepatitis and extrahepatic biliary obstruction, particularly during the phase when hepatitis exhibits obstructive phenomena. Review of the data, however, suggests a considerable overlap between the various types of hepatic disease, and it seems likely that further application of this test in specific instances is necessary to determine its diagnostic value.

Drugs.—The incidence of hepatitis from chlorpromazine is difficult to ascertain. At least two groups of authors have reported their observations with respect to the clinical and pathologic stigmata of this drug (221, 222).

One group cited the incidence as 5 per cent. The hepatitis seems similar in all respects to the well-known methyltestosterone hepatitis and in many respects it simulates the findings in jaundice due to mechanical obstruction of the extrahepatic biliary ducts. Thorough consideration should be given before surgical treatment is advised for a patient in whom jaundice develops during treatment with chlorpromazine.

The same microscopic findings and laboratory picture have been seen with use of thiouracil, methyltestosterone, methimazol, phenurone, and arsphenamine. Interesting microscopic findings have been reported by Liber & Barshay (223) in the case of a patient receiving para-aminosalicylic acid for pulmonary tuberculosis. Despite absence of clinical evidence of hepatic disease there was an extraordinary degree of multiplicity and multilobarity of the nuclei and hepatic cells, associated with leukocytic infiltration, focal necrosis, and other evidences of hepatitis. This may be specific evidence of a PAS hepatitis. Pentobarbital sodium, in hypnotic doses, was given to patients with severe hepatic disease and to controls, but evidence was not obtained that patients with hepatic disease were more sensitive to the drug or that removal from the blood was delayed. Despite the common use of chloral hydrate or paraldehyde for sedation in hepatic disease, Sessions and co-workers (224) have called attention to the fact that there are no clinical studies showing that these drugs are particularly innocuous or that other sedatives really do harm to the liver.

Other Problems

Acute hepatic insufficiency in the chronic alcoholic seems to be associated with a typical hepatic lesion characterized by hyalin degeneration, necrosis of hepatic cells, and parenchymal disorganization which is distinct from the usual fatty liver and commonly responsible for fatal hepatic insufficiency (225). In cases of multiple myeloma in which elevation of globulin is frequent, the cephalin flocculation and thymol turbidity tests frequently give normal results according to Walsh, Humoller & Zimmerman (226). Previous observations that abnormalities of the cephalin flocculation test are related to elevation of gamma globulin and potentiated by hypoalbuminemia may be an oversimplification when applied to multiple myeloma. Clinically, marked hyperglobulinemia associated with normal thymol activity and negative cephalin flocculation does not appear to be attributable to lupus erythematosus and probably not to sarcoidosis, but it is usually suggestive of multiple myeloma. Some physicians consider cirrhosis of the liver an indication for surgical treatment in the patient with ulcerative colitis. It is reported by Parker & Kendall (227) that the liability to development of cirrhosis in these patients as compared with that of the population as a whole is not increased. Others have reported an incidence ranging from 3 to 19 per cent. From the Armed Forces' Institute of Pathology comes the report by Dubin & Johnson (228) of a possible new type of hepatic disease characterized by the deposition of a pigment within the hepatic parenchymal cells,

yet unidentified, but having certain histochemical properties in common with ceroids and lipochromes. Clinically, nothing specific was evident, but the patients seemed to have moderate jaundice of long duration, more than the usual amount of abdominal pain, and the prognosis in general seemed excellent.

GALLBLADDER AND BILIARY DUCTS

It is reported by Pines & Rabinovitch (229) that acute perforation of the gallbladder occurs in 6 per cent of the patients having acute cholecystitis. The authors discourage the belief that rupture is rare and that perforation is not a hazard because it is promptly sealed off. The mortality rate was nearly twice as great among patients with noncalculus cholecystitis as among those with stones when perforation occurred. Further studies by Fortner & Kohen (230) have confirmed the earlier observation that gallstones can be formed in Syrian hamsters which are fed a nearly fat-free test diet. The gallstones are composed principally of crystalline cholesterol. This experimental method of production may prove important in investigation of causative and modifying factors in the formation of gallstones. The incidence of pseudoalbuminuria was found to be 15 per cent; the condition persisted as long as several days after iodalphionic acid (priodax), iopanoic acid (telepaque), iophenoxic acid (teridax) and other gallbladder dyes were administered [Seedorf and co-workers (231)]. Hot Exton's reagent was the test material. The incidence was 50 per cent with cooling when tetraiodophenolphthalein was used; this suggested that pseudoalbuminuria was probably commoner than was realized in the earlier days of cholecystography. Howard (232) informs us that after severe injuries to any part of the body, not necessarily to the abomen, cholecystography frequently is temporarily unsuccessful and the gallbladder cannot be visualized on the roentgenogram. The only explanation offered is that perhaps the gallbladder participates in the body response to injury. Appraisal of intravenous cholangiography continues. Tomography is considered an aid in removing confusing overlying shadows owing to gas from the bowel (233). In the surgical treatment of choledochal cyst, it is emphasized that either excision or marsupialization is associated with an excessive mortality rate. Simple anastomosis of the cyst with the duodenum or by means of a Roux Y is attended by a significantly lower mortality. In cases of Adams-Stokes disease with syncope of cardiac origin, significant benefit has been obtained, according to McLemore & Levine (234), by cholecystectomy when cholelithiasis is present.

DISEASES OF THE PANCREAS

Wheat (235) has written a comprehensive review of the literature of 1953 that concerned the pancreas. Patients with mucoviscidosis were noted to excrete approximately 106 mEq. of chloride and 133 mEq. of sodium per liter of sweat. This is rather excessive. The normal person loses an average of 32 mEq. of chloride and 59 mEq. of sodium.

Silverman & Shirkey (236) report that lipiodol given orally has been used as a test to determine the presence of pancreatic lipase in children with fibrocystic disease. If the lipiodol is digested, the urine will contain iodine. No patient with fibrocystic disease of the pancreas proved to have positive results to a test for iodine in the urine in a dilution greater than 1:2. A dilution of greater than 1:4 seemed to exclude fibrocystic disease. Nothmam, Pratt & Callow (237) reported that the fat-splitting enzyme, lipase, was found in the urine in large amounts immediately after ligation of the pancreatic ducts. Pancreatectomy causes a disappearance of the enzyme from the urine. The high values of urinary lipase that occurred after ligation of the pancreatic ducts disappeared promptly when the pancreas was removed. The fat-splitting enzyme of the urine probably is identical with the pancreatic lipase. In dogs Dragstedt and co-workers (238) maintain that the pancreas seemed to exert a proximal effect on the regulation of lipides in the blood by means of an internal excretion, lipocaic, which potentiated the lipotrophic effect of choline and similar substances in the diet. In the absence of the pancreas or when its endocrine function is impaired, the presence of pancreatic juice in the intestines caused hyperlipemia and high insulin requirements.

A study by Dreiling, Greenspan & Sanders (239) showed that increased serum mucoprotein and antithrombin levels occurred in about half of the patients with pancreatic disease. Elevations of the concentration of antithrombin were not related to the increases in the serum mucoprotein. The antithrombin titer was abnormal in 25 per cent of 49 patients without pancreatic disease and normal in 50 per cent of a series of 30 patients with true pancreatic disorders. Increased antithrombin titers were found in six of 11 patients with acute pancreatitis. Normal antithrombin titers occurred in the presence of proved acute pancreatitis. In the diagnosis of pancreatic cancer and chronic pancreatitis, results of the secretin test had greater value than the value for serum amylase and the antithrombin titer. The latter determinations, that is, those for serum amylase and the antithrombin titer, however, may be of assistance in patients with acute pancreatitis in whom testing with secretin is not clinically feasible. The response of amylase in the blood to provocative tests in which morphine, secretin, metacholine, and bethanechol were used singly and in combination in 192 patients, with and without proved pancreatic disease, indicated that these response tests of serum enzymes have no value in the diagnosis of pancreatic disorders (240). Althausen & Uyeyama (241) described a new test of pancreatic function based on a comparison of the amylolytic activity of pancreatic juice in the intestine on a test dose of starch and glucose. The test was positive in 87 per cent of a group of patients with known chronic pancreatitis. A similar test on the proteolytic activity of pancreatic juice in the intestines failed to yield helpful results in the diagnosis of pancreatic disease.

Plasma amylase was studied by Culotta & Howard (242) in patients in a stage of acute alcoholism. None of the patients had symptoms suggesting pancreatitis. Six of 51 patients had concentrations of amylase in the serum

which were higher than normal. Perhaps it is in these people who use alcohol that pancreatitis later develops. In a study of the secretin test by Dreiling & Richman (243), it was found that in addition to its value in the diagnosis of pancreatitis, it may be of value in determining the patency and the function of the biliary tract in such conditions as obstructive jaundice, postcholecystectomy syndrome, diarrhea, and colitis. Sommers, Murphy & Warren (244) found that patients dying of carcinoma of the pancreas frequently (41 per cent) had hyperplasia of the pancreatic duct. This condition was found in 28 per cent of patients with diabetes and 6 per cent of normal persons. The endocrine-stimulated organs and the gastrointestinal tract were involved in 36 per cent of the patients who had multiple primary cancers and hyperplasia of the pancreatic duct. It would seem that the dictum that diabetics are more likely to have carcinoma of the pancreas may be accurate. Smith asserts (245) that the differential diagnosis of acute pancreatitis and intestinal obstruction may be difficult for in each condition elevation of the concentration of serum amylase may be found. Intestinal obstruction rarely caused this concentration to be greater than 1,000 Somogyi units. Acute pancreatitis may cause electrocardiographic changes simulating those of myocardial infarction (246). These changes may be due to fat necrosis of the myocardium, but the actual reason is unknown. In acute necrotizing pancreatitis, cyanosis and albuminuria have been prominent and puzzling findings. In six cases, one of which was thoroughly studied, Lynch (247) found that fat emboli involving the kidneys, lungs, and brain seemed to be the etiologic factor. This point has possibly been missed in the past because the high-lipase titer of the blood may have led to splitting of the fat so that it failed to take the neutral fat stain.

Nothing new has been suggested regarding the treatment of pancreatitis. Zollinger, Keith & Ellison (248) found that 12 patients with acute pancreatitis and 16 with chronic pancreatitis had an average deficit of whole blood volume of 30 per cent. Serum albumin was helpful in the treatment. This may be related more to improving the blood volume than to neutralizing the trypsin. Most clinicians feel that the patient with acute pancreatitis should not undergo surgical exploration. If it is correct that the disease is often fatal because of the continued reaction of the ferments, as DeNicola (249) maintains, then perhaps the condition should be considered analogous to other acute illnesses accompanied by shock. After a period of medical observation and surgical preparation, the abdomen with its ferments, debris, and blood products should perhaps be drained. In patients with chronic relapsing pancreatitis, Duval (250) suggested that caudal pancreaticojejunostomy may be a useful surgical approach.

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HEMATOPOIETIC RESPONSES TO RADIATION INJURY[1]

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Introduction

Evidence has been accumulated by a number of investigators that suggests that a factor(s), present in certain biologic material, has a specific value for the treatment of radiation injury even when administered after irradiation. Demonstration of the postirradiation efficacy of this factor(s) is as yet confined to experimental animals and has been shown to apply in mice (1 to 4), guinea pigs (2), rabbits (5, 6), rats (7, 8), and dogs (9). Until recently (vide infra), the only effective source of the factor has been found to be hematopoietic tissue or hematopoietic-containing tissue. It is not accepted generally that the effectiveness of shielding or the injection of hematopoietic-containing tissue lies in the production or release of a noncellular substance or group of substances by the shielded or injected tissue. Some investigators maintain that the data reported thus far do not eliminate the possibility that the shielded or injected tissue provides cellular precursors that are capable of colonizing the depleted tissues, at least temporarily, maintaining the irradiated animal in a condition that permits normal cellular regeneration and functional reconstitution to occur (10, 11). Survival of an irradiated rodent, which has been given a suspension of hematopoietic cells, is correlated roughly with the rapidity of hematopoietic regeneration in the animal, but it is not known with any degree of certainty if systems other than the hematopoietic benefit directly from the shielded or injected tissue (11 to 13). It has been amply demonstrated that above a given dose of total-body x-radiation (mice, circa 1500 r), shielding of the spleen or injection of hematopoietic tissue does not prevent death of the animal (14). In point of fact, Williams & DeLong (15) have shown that deaths occurring after exposures above 1500 r are due primarily to damage to the intestinal tract.

In 1949, Jacobson and his co-workers (16) demonstrated that lead shielding of the surgically exteriorized spleen of mice during total-body x-irradiation markedly enhanced survival. The same authors found that under these circumstances the blood-forming tissue, though destroyed by irradiation, recovered in a very short time. It was later shown that transplantation of homologous spleens or embryonic tissue, or the intraperitoneal or intravenous administration of cell suspensions from these sources given in the postirradiation period likewise had a salutary effect upon survival of the mouse and the recovery of its blood-forming tissue (1). Lorenz and his associates (2, 17) described a similar result with homologous bone marrow suspensions and later reported comparable results with heterologous tissue (rat marrow to mouse and guinea pig marrow to mice) (18). The work of these and other investigators has been reviewed comprehensively (10, 13, 19, 20, 21).

[1] The survey of the literature pertaining to this review was completed in September, 1955.

The Humoral Factor

On the basis of a number of suggestive experiments, Jacobson postulated the so-called humoral theory of recovery from radiation injury (1, 22). The humoral theory as it has been presented implies that the shielded or injected viable hematopoietic tissue produces a substance or group of substances that are required or utilized by the irradiated cells of the recipient for the resumption of certain functions that were inhibited by irradiation. Support for this theory has been based on indirect evidence that has been reviewed critically by Loutit (10) and others (20, 21). The evidence that is the most convincing may be summarized as follows:

Homoplastic and heteroplastic regeneration of hematopoietic tissue.—Such regeneration occurs in spleen-shielded mice or in mice that have been given transplants or cell suspensions (1). This type of regeneration in animals recovering from an LD50[2] of x-radiation has been described repeatedly in the literature by a number of authors including Bloom (23) and Block *et al.* (24). In other words, it is a normal mechanism of recovery. In animals that have been spleen-shielded or that have been injected with cell suspensions of hematopoietic origin, recovery occurs in a manner that is identical, from a histopathologic point of view, to that observed during the regenerative process except that it begins earlier and is complete in a shorter interval of time.

A more or less reproducible pattern of hematopoietic destruction, atrophy, and regeneration occurs in the animals that survive an x-ray LD50. In the mouse, active, sustained, orderly regeneration begins at about six days following such an exposure. The pattern of response of mammals to total-body irradiation is essentially similar if differences in species sensitivity are taken into account. For example, exposure of the rabbit to 800 r (30-day LD50) produces the same general effect on the blood-forming tissue as does 600 r (LD50) in the mouse. Doses of lesser magnitude produce less destruction, and the capacity to regenerate and to perform other functions are inhibited for less time.

In general, the histologic findings in the blood-forming tissue after exposure to a median lethal dose of x-radiation are reflected fairly accurately in the peripheral blood. A description of the histologic changes is conventionally divided into 3 phases, namely (*a*) destruction, (*b*) atrophy, and (*c*) regeneration. Descriptions of the atrophic phase often imply that no free hematopoietic cells remain in the hematopoietic tissue of an animal that has been exposed to an LD50 or above. That production of the various cell types never ceases completely is clear from their presence in the circulating blood in small numbers throughout the stage of atrophy of the blood-forming tissue as a whole. Nevertheless, it is difficult, if not impossible, to assess with any degree of accuracy the relative contributions of the basic reticulum and the free residual precursors to the total regenerative process. It is obvious that, after a median lethal dose (or less), recovery of blood-forming tissue of the survivors occurs spontaneously. Estimates of the number of free precursors present during the atrophic stage in the marrow alone far exceed

[2] The radiation exposure after which half of the animals die during a 28-day period of observation.

the quantity necessary to initiate recovery if such elements are introduced intravenously. One must therefore assume that the basic reticulum and the free precursors in the hematopoietic system or tissue of irradiated animals are incapable of originating orderly regeneration during the period that is roughly dose-dependent. After a total-body exposure of rabbits or mice to 100 r, this inhibition is short lived; after an LD50, it is circa 8 days; and after 1000 r or more, inhibition continues until death of all the animals at 12 to 14 days.

With the intravenous introduction of a total of 3×10^6 cells (bone marrow, spleen, or 14-day embryonic liver) or less immediately after irradiation of the recipient mouse, regeneration is initiated by the fourth or fifth day in lymphatic tissues and in the bone marrow (25). Heteroplastic regeneration in the marrow is especially prominent under these circumstances and cannot be explained on any other basis than the release of the reticulum from inhibition. The contribution of residual free precursors to regeneration in the marrow and lymph nodes can likewise only be explained on this basis. The introduction into the irradiated animal of a small number of whole cells from such homologous sources as mentioned above may well contribute to repopulation of depleted tissue by multiplication and division, but unless these introduced cells are involved directly or indirectly in the release of the basic reticulum and free residual precursors, then it can only be assumed that the introduced cells are entirely responsible for repopulation. Complete regeneration of the hematopoietic tissues under these circumstances is accomplished many days before spontaneous recovery begins, if indeed (depending on initial irradiation dose) it begins at all.

The humoral theory is strengthened materially when the data are considered in the light of the fact that heterologous bone marrow (rat to mouse) induces hematopoietic regeneration in the irradiated animal and increases its chances for survival.

The minimal number of living cells required in an injection to bring about significant recovery of the mouse after an LD99 (900 r) of total-body x-radiation has been shown to be about 50,000 (26). This number is small when one recalls that the circulating peripheral blood contains normally between 5 to 10×10^3 white cells per $mm.^3$. The source of the cells is important. Normally circulating cells of the order of 5 to 10×10^6 have no appreciable effect on the survival of irradiated mice, although this amount from bone marrow, young mouse spleen, or embryonic mouse liver is effective (26). The relationship between number of cells injected or shielded is not linear. After an LD99 of 900 r, survival following the injection of 50,000 cells from the embryonic mouse liver or baby spleen is about 20 per cent. Both survival and the rapidity of hematopoietic regeneration are augmented with increasing increments of cells from these sources up to about 10×10^6, which gives 75 per cent survival. Above this quantity, no further appreciable enhancement of survival or hematopoietic regeneration is noted.

The cell type most important in bringing about recovery under these circumstances, if one type is responsible, has not been determined. It is a fair assumption, in view of the failure of normal peripheral mouse blood at 5 or 10×10^6 cells, to favorably influence survival or hematopoietic regeneration,

that the more primitive tissue of the hematopoietic system is involved. The homologous tissue studied thus far, e.g., spleen cells, embryonic liver tissue, bone marrow, and bone spicules (18), all may be considered to contain hematopoietic tissue or potential hematopoietic tissue. For example, transformation of bone cells to osteoblasts and of osteoblasts to hematopoietic cells has been described (27).

Heterologous tissue transplants or cell suspensions.—These have been reported by Congdon, Lorenz, and co-workers (18, 28) and Jacobson *et al.* (29) to have a significant effect on the survival and hematopoietic regeneration of irradiated recipients. Jacobson first described evidence that suggested the effectiveness of mouse spleen transplants on recovery of the blood-forming tissue of irradiated rabbits (1). Congdon & Lorenz reported that rat bone marrow and rat bone had a significant effect on the survival of irradiated mice (28) and that guinea pig marrow likewise afforded a significant effect on the survival of irradiated mice (18). Jacobson and co-workers (29) and Cole *et al.* (30) have corroborated the effectiveness of rat marrow on the survival of irradiated mice, whereas Loutit has been unable to confirm findings of these investigators with heterospecific material (10). More recently Jacobson *et al.* (31) reported that the injection of cells from the embryonic mouse liver or baby mouse liver or spleen enhances the survival of irradiated rabbits. This latter study shows that hematopoietic cells from the mouse are as effective in promoting recovery in the irradiated rabbit as are cells from the rabbit. This tends to explain the findings of several investigators; namely, that the effectiveness of shielding or cell injection measures varies greatly from species to species and even from strain to strain within the same species (32, 33, 34). This has been interpreted by Jacobson as representing differences in the capacity of the hematopoietic tissue from certain species to produce the recovery factor. Loutit (10) has focused attention on the late deaths and has suggested that heterologous material, when injected, may "take" as a graft and that the late death of the animal might be due to the development of isoantibodies in the host that eventually kill the graft and the animal. On the basis of this concept and other evidence Loutit maintains that proof of the humoral theory is still lacking.

Cell-free preparations of hematopoietic tissue.—Cole *et al.* (19) have reported that cell-free preparations of hematopoietic tissue increase survival of mice given lethal doses of x-radiation. These investigators attempted to ascertain the nature of the factor prepared from mouse spleen by the use of a Potter-Elvehjem type of all-glass homogenizer. Their preparation served as a reliable reproducible source of material, which invariably gave 100 per cent survival if it was injected soon after a dose of x-radiation that ordinarily produces death in all of the mice exposed to it. Using spleen mash or cell suspensions, Jacobson and his associates (35) observed not only increased survival but accelerated weight gain and enhanced hematopoietic regeneration. Cole *et al.* further found that the effective material resided in the centrifugal residues and sought to determine whether the activity might be associated with the intracellular components. They fractionated the homogenate in sucrose by ultracentrifugation and found that only the fraction containing what they interpreted to be nuclei and nuclear fragments was effec-

tive upon assay. No protective effect was obtained with the mitochondria, microsomes, or soluble supernatant fraction. On the basis of enzyme studies, the Cole group postulated that the active principle is a deoxyribonucleoprotein because it is susceptible to the action of deoxyribonuclease and trypsin and is resistant to ribonuclease. They were unable to demonstrate the factor in liver or thymus but found it by their methods in spleen and bone marrow. On the other hand, Jacobson *et al.* (35) have demonstrated activity in fetal mouse liver, young mouse liver, and, to a lesser extent, in adult mouse liver. Loutit criticized the work of Cole on the grounds that no cell-free solutions of deoxyribonucleoprotein have been used successfully to enhance the survival of irradiated animals (10). Goldwasser *et al.* (36) has been unable to obtain data that confirm Cole's interpretation in this latter respect.

In view of the fact that 50,000 spleen cells are all that are required to enhance survival of irradiated mice, less than 1 per cent survival of whole cells from 380 mg. of spleen in a preparation made according to Cole's technic would still contain more than 6.4×10^6 living cells. Simmons & Jacobson (37), in an attempt to test Cole's approach, subjected a leukemic spleen from DBA mice to Cole's technic and found that, upon injection of this preparation, 100 per cent of the injected DBA recipients died of leukemia. This implies that treatment of leukemic cells by Cole's technic does not eliminate the required number of whole cells and is therefore not comparable to such treatment of normal spleen or that, under the conditions of Simmons' experiments, the leukemic agent was indeed present in the cell nuclei fraction, or naked nuclei. It is also possible that viruses capable of inducing the leukemia were released. The approach of Cole is attractive and offers interesting possibilities for speculation. Like evidence proposed by Jacobson to support the humoral theory, Cole's hypothesis cannot be accepted at this moment as proof that the humoral theory is correct. If his concept is correct, there still remains the task of isolating, identifying, and stabilizing the nucleoprotein responsible because there is, in all probability, a multitude of nucleoproteins in the mammalian nucleus.

There is some evidence that hog pyloric mucosal preparations from which most of the protein has been removed by precipitation with 50 per cent ethanol have a significant effect in the reversal of the lethal effects of x-radiation in mice. The active materials in these soluble preparations appear to be substances of low molecular weight since they pass through an ultrafilter (38).

Relationship of the Recovery Factor to Experimental Leukemia

Furth (39), Kaplan (20), Law & Miller (40), Lorenz & Congdon (13), and Simmons & Jacobson (37) have reported a number of interesting observations that may bear some relationship to the so-called recovery factor. Furth (39) first demonstrated that the incidence of lymphoma in suceptible strains of mice was reduced markedly by thymectomy. Kaplan, who has done such outstanding work in this field, has reviewed his own contributions and those of others (20). He has shown that the high incidence of lymphoma or lymphatic leukemia induced in C57BL mice by exposure to total-body

x-radiation can be reduced markedly by thymectomy. This observation and that of Furth are especially interesting in view of the fact that thymic cells have been reported by Cole *et al.* (19) and Goldwasser *et al.* (36) to be ineffective in reversing the radiation syndrome, whereas spleen or marrow cells will do so consistently. On the other hand, thymectomy prevents the incidence of certain spontaneous as well as radiation-induced lymphomas and leukemia, whereas bone marrow or spleen cells or spleen-shielding greatly reduces the incidence of tumors, as demonstrated by Kaplan (20), Law & Miller (40), and Lorenz & Congdon (13). Using DBA leukemia cells, Simmons & Jacobson (37) have shown that acute leukemia induced in CF No. 1 mice, weakened by total-body exposure to x-radiation and injected with DBA leukemic cells, can be prevented entirely by spleen-shielding of the host. Cortisone (41, 42) also reduces the incidence of spontaneous and induced lymphoma and leukemia in mice. It is difficult, if not impossible at this time, to explain adequately in simple terms these various seemingly related findings.

The incidence of leukemia has been found to be significantly increased among the atomic bomb victims in Hiroshima and Nagasaki (43, 44). This information is interesting when considered in the light of the results of laboratory experiments that show the high incidence of leukemia in irradiated mice (13, 45) and guinea pigs. One cannot refrain from wondering if the mechanism of the production of leukemia in the human being and the experimental animal is similar under these special circumstances, and if the spontaneous and induced leukemias may well be amenable to the influence of the so-called recovery factor.

Relationship of the Recovery Factor to Immune Mechanisms

It has been demonstrated that the capacity to produce antibodies to an injected particulate antigen is retained by irradiated animals if they are spleen-shielded during the exposure (46). This capacity has also been observed in irradiated animals injected with spleen cells (47). The data suggest that the functional reconstitution of cells involved in antibody production is susceptible to the recovery factor. The recovery of the blood-forming tissue and the capacity to produce natural and immune antibodies undoubtedly act synergistically in bringing about survival of irradiated animals that have had the benefit of spleen-shielding or have been injected with hematopoietic cells in the postirradiation period. The restoration or continued production of natural antibodies or other factors involved in "natural resistance" may well explain the findings of Simmons on leukemia and may, of course, be related to the interesting demonstration by Pillemer and his associates (48) that circulating properdin (euglobulin) is reduced in irradiated animals. Pillemer has also reported that the administration of properdin to animals exposed to radiation in the LD90 range significantly increases survival.

Concluding Comments

The evidence available concerning the recovery factor supports but fails to prove the hypothesis that a humoral agent, rather than only the proliferation of the shielded or injected cells of hematopoietic origin, is responsible for the recovery of animals subjected to total-body x-radiation in the lethal

range. That animals die when given dosages above 1500 r even though cells of hematopoietic origin are administered indicates the limitation of this approach at the present time to the practical problem of protecting the mammal against lethal amounts of radiation. On the other hand, the simple fact that the introduction of normal cells or their products into the irradiated animals can reverse *in vivo* tissue inhibition or tissue destruction by irradiation and that such tissue more quickly assumes previous functions, e.g., antibody production or proliferation, introduces many avenues of exploration for the radiobiologist.

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NEOPLASTIC DISEASES (CANCER)[1]

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This chapter is dedicated to the memory of our friend, G. B. Silver, M.D., an outstanding physician devoted to the field of cancer, deceased in August, 1955.

The trends in experimental cancer research have been extensively reviewed by Haddow in the last *Annual Review of Medicine* (1). Important changes are taking place in the management of cancer patients and a crossroad is being approached which warrants a statement of current opinions and results of tumor therapy. The refinement of diagnostic tools for early cancer detection, the development of newer and the extension of older surgical techniques, the availability of more powerful equipment to deliver ionizing radiation and the progress in hormone-chemotherapy warrant this emphasis on problems of clinical cancer.

Clinical Studies

Breast.—The changes in the management of patients with carcinoma of the breast illustrate well the point emphasized in the introductory remarks: a radical departure from the conventional methods is evolving in the therapy of early and advanced cancer of the breast. A monograph on this subject has been recently published (2). The indications for surgery and for radiotherapy in early stages have been better defined and newer surgical approaches are being applied to properly selected advanced cases. Until recently, radical mastectomy was the generally accepted method of treatment for early breast carcinoma, using the criteria of operability described by Haagenson (3, 4) and by Haagenson & Stout (5). Radiotherapy was rarely given pre-operatively, and postoperatively only when the axillary lymph-nodes were involved. However, the five year survival of patients with cancer of the breast in teaching hospitals was only 35 per cent and the ten-year survival 20 per cent whether the patients were treated surgically alone or in combination with radiotherapy (6, 7). The statistics of the Mayo Clinic based on 4637 patients are of interest since the survival was followed up to 40 years postoperatively: the over-all 15-year survival was 25 per cent, the 35- to 40-year survival 6.6 per cent, and the corresponding figures for patients without axillary node involvement were 48 per cent and 14 per cent, respectively (8). Because of the dissatisfaction with these results, search for the causes of the failure and for improved forms of treatment continued. The advisability of spending large sums of money for early detection was even questioned. It was claimed that the determining factors in the prognosis were the aggressiveness of the tumor and the resistance of the host

[1] The survey of the literature pertaining to this review was completed in August 1955.

rather than the early detection or the form of therapy. However, the reasons for some of the therapeutic failures became obvious. Andreassen, Dahl-Iversen, & Sørenson (9) demonstrated that 33 per cent of patients with tumor involvement of the axillary lymph nodes had occult supraclavicular nodes. Handley (10) found involvement of the internal mammary glands in 48 per cent of patients with axillary node involvement. Urban and Baker reported similar findings. Wyatt *et al.* (11) studied 60 specimens obtained by extended radical mastectomy with en-bloc dissection and excision of the sternal ends of the second to fourth ribs in patients who seemed to meet the "classical" criteria of operability; the internal mammary nodes were involved by tumor in 19 patients. Lewison believes that the presence or absence of axillary node involvement by tumor is the most important prognostic factor for patients with carcinoma of the breast (12). The lymph drainage of the breast was studied by injecting radioactive colloidal gold into the breast pre-operatively; approximately 90 per cent of the radioactivity localized in the axillary and 10 per cent in the internal mammary lymphnodes, irrespective of whether the isotope was injected into the inner or outer quadrants of the breast, while no radioactivity was found in lymphnodes replaced by tumor (13). The difficulty of assessing the presence of involved axillary nodes is well known; Haagenson *et al.* have reexamined the lymphnodes of resected specimens previously judged to be free of tumor and found a significant number of lymphnode metastases (14). On the basis of this knowledge the low survival rate following the conventional radical mastectomy became understandable since surgery was performed when the disease was beyond the surgeon's reach and radiotherapy was applied to too few sites and in dose levels which were usually not cancericidal.

McWhirter reported on 1182 patients treated by simple mastectomy and radiotherapy. The over-all five-year survival rate was reported to be 42 per cent, while for the "operable" group it was 58 per cent, and the ten-year survival was 39 per cent (15). In Helsinki 127 patients without clinical evidence of lymphnode involvement were treated by the McWhirter technique; 84 per cent survived five years and 72 per cent 10 years (16). At St. Bartholomew's Hospital, 1044 patients with carcinoma of the breast were followed up to 15 years (17); five- and ten-year survival rates for patients in Stage I were 72 and 51 per cent, and for those in Stage II 39 and 26 per cent, respectively. No significant difference was noted in the survival rates of the groups treated with radical mastectomy from those treated with local excision or simple mastectomy followed by radiotherapy. Therefore, these authors conclude that whenever efficient radiotherapy is available radical mastectomy should not be performed (17). On the basis of the results obtained with the McWhirter technique Garland (18a), as well as an editorial in *Radiology* (18b), urge that this method be given an adequate trial in the United States. The importance of the biological behavior of the tumor and of the resistances of the host are well-illustrated by the St. Bartholomew study; although the tumor was present for longer than two years in 31

per cent of the patients, they were still in Stage I, while 19 per cent of those with a history of only one month or less were already in Stages III and IV when first seen. Haagenson acknowledges in his latest publication (7) the fine results obtainable with the McWhirter technique and opposes the super-radical surgical attack (9, 19 to 21). However, he advocates the carefully performed radical mastectomy whenever his criteria of operability are met and suggests radiotherapy for all others. He performs radical mastectomy only when biopsies of lymphnodes of the apex of the axilla and of the first intercostal space are free of tumor. This careful screening reduces significantly the number of patients in whom surgery should be performed but provides those properly selected with the best chance of a long survival (7). Ackerman studied 719 consecutive patients of McWhirter and states: "McWhirter has not put in jeopardy the well-planned radical mastectomy for the patient with operable breast cancer" (22).

Recently, several reports have appeared on the management of disseminated breast cancer. The previously reported advantages of dehydrotestosterone (less virilization) over testosterone have not been substantiated (23 to 25). The value of bilateral adrenalectomy has been appraised by Huggins in 100 patients; improvement was noted in 40, and considerable regression without relapse for 1 to 3 years in 15 patients (26). Randall (27) and Galante *et al.* (28) report the results obtained in breast cancer patients so treated; eight of the 14 patients of the former and 22 per cent of 29 patients of the latter showed objective improvement. The patients best suited for this procedure, according to Huggins, are those with adenocarcinoma who had an interval of freedom from metastases for at least three years after radical mastectomy. Pearson comments that patients who previously responded to oophorectomy are likely to respond to adrenalectomy and emphasizes the value of calcium excretion studies in the screening of patients, differentiating the estrogen-dependent and therefore adrenal-dependent tumors from those which are autonomous (29). Hypophysectomy was performed in 37 patients and objective improvement was noted in one-third of the cases (30). Simplifications of hypophysectomy are being explored by the insertion of radon seeds into the pituitary fossa (31), so far performed in nine patients, by the injection of radioactive chromic phosphate (32) and of radioyttrium into the hypophysis (33).

Cervix and uterus.—Exfoliative cytology, as evolved by Papanicolaou (34), led to the detection of an increasing number of asymptomatic cases of pre-invasive carcinoma of the cervix, carcinoma *in situ*. Dahlin *et al.* (35) examined cervical smears of 30,310 normal women and found 270 or 0.89 per cent unsuspected malignancies. Of all cases of squamous cell carcinoma, 90 per cent were *in situ*. The average age of these patients was 42 years; it was 49.7 years in those with infiltrating carcinoma. When the same group was re-examined one year later 0.17 per cent "new" cancer cases were found. Whether these were missed at the previous examination or developed in the interval between the two examinations is difficult to ascertain. Pre-

liminary data from mass screening of the entire female population in the Memphis area (200,000 women) are now available (36, 37). Cytologic studies were completed in 90,000. The smear was positive or suspicious for malignancy in 1.8 per cent, and 88 per cent of the cases which were positive on smear and proven on biopsy were unsuspected clinically. A large percentage of the positive cases had cancer in the pre-invasive stage. The average age of these patients was considerably younger—33 years; of those with invasive carcinoma the average age was 52 years. One year later 25,000 patients were reexamined and a considerably smaller percentage of positive or suspicious smears were detected. This may again represent new cases or those missed at the previous examination. These two mass studies illustrate the feasibility of the cytologic screening program, employing trained technicians to screen the smears and competent pathologists to check the suspicious or positive slides. Attempts are also being made to develop mechanical devices to facilitate extensive cytologic screening procedures (38).

The early transformation of epithelial cells of the cervix and vagina of mice from acute and chronic inflammation to dysplasia, noninvasive and invasive carcinoma following the application of 3,4-benzpyrene, have been described; a good correlation between exfoliative cytology and histology was noted (39). The importance of exfoliative cytology lies in the fact that it helps to detect the disease in the asymptomatic pre-invasive stage in which even an adequate biopsy may suffice to cure it (40). A study of cytologic, histologic, and clinical correlation of carcinoma *in situ* is contained in an article by Fennel & Castleman (41). Data are also available in the literature which indicate that a high percentage of early cases is curable by radiotherapy alone. Only 12.2 per cent of the patients seen at Radiumhemmet (42) were in Stage I; the recovery rate by radium application in this stage was 71 per cent while 52.4 per cent of the cases were in Stage II and had a recovery rate of 50.3 per cent. The recovery rate of Stages III and IV was considerably lower, 24.7 and 9.1 per cent, respectively. Similar results were reported by Way (43). It is certain that a larger number of patients with carcinoma *in situ* or in Stage I could be detected by more extensive use of exfoliative cytology.

In this connection the work of the Grahams (44) is of interest. They were able to correlate and predict the responsiveness to radiotherapy on the basis of changes of the normal vaginal cell constituents during and after radiation therapy. For instance, 65 per cent of cases with marked radiation changes of the normal cells lived five years, whereas only 8 per cent of those with poor cell response lived for this period of time. However, those with a poor cell response still had good results with surgery, and 74 per cent of such patients, in Stage I, lived five years postoperatively. This cellular index of radiation sensitivity has aroused considerable interest. Confirmatory results have been reported by several groups (45 to 50), negative ones by others (51 to 54), and Deder (55) concludes that the described changes are probably artifacts due to changes of cellular viscosity caused by radia-

tion, but are still useful in predicting the radiosensitivity of the tumor.

In view of the good results of radical surgery (56) it seems that such an approach may find its widest use in the treatment of cases which fail to show response to radiation shortly after its completion (43), or in those with local recurrence with and without lymphnode involvement (57). Since the progress of the disease and the results of therapy can now be serially followed by exfoliative cytology of tumor- and probably also of normal-cells, surgery can be instituted after unsuccessful radiotherapy without undue delay. Studies also indicate that whenever the primary growth responds to radiotherapy, the involved lymphnodes seem to respond equally well and vice versa (43).

Sherman & Arneson (58) report 19 patients with cancer of the endometrium who were treated with intracavitary radium by the Heyman method and then by hysterectomy; the five-year survival was 75 per cent. Similar results were obtained in seven patients treated with radium alone.

Of interest is the observation that the vaginal epithelium shows more cornification in cases of carcinoma of the cervix and corpus than in the corresponding controls, this difference being more marked in cases of corpus carcinoma (74 vs. 27 per cent), indicating a high estrogen level in these patients (59). Control of profuse discharge and bleeding in far advanced carcinoma of the cervix was obtained by stilbestrol, although the tumor growth was not checked (60).

New sources of radiation have been used such as irridium, which has a less penetrating radiation spectrum than radium and may thereby cause less radiation damage to the rectum and urinary bladder (61), as well as megavolt external radiation (62, 63).

Lung.—A remarkable increase in the incidence of carcinoma of the lung has occurred in the past decade, both in males and females, which cannot be accounted for by better diagnosis or increased longevity alone (64 to 68). Evidence has been presented that tumors occur most frequently at sites of the respiratory tract where inhaled particulate matter is deposited; tobacco residue was deposited in the most dependent segments of a model bronchial tree (69).

Carcinoma of the lung is more frequent in urban than in rural areas; McKinley, quoted by Clemo *et al.*, reports a ratio greater than 2:1 in Scotland (70). Blacklock *et al.* (71) analyzed 50 specimens of human lungs; they found no appreciable difference in the carbon content of lungs with and without tumor. However, the carbon content of lungs of city dwellers was higher than that of those in rural areas and the increase was related to the length of time of exposure.

The increase in the incidence of carcinoma of the lung presents a puzzling problem. Is it due to tobacco, air pollution, or to other factors as yet unknown? The relationship between tobacco consumption and incidence of carcinoma of the lung has been amply documented by statistics from several countries (65, 66, 72 to 75). In view of the strong statistical correlation

between cigarette consumption and carcinoma of the lung, attempts have been made to produce lung cancer in experimental animals with various tobacco products. However, these attempts were unsuccessful. Wynder *et al.* produced skin cancer by painting (76, 77), and Holsti & Ermala (78), carcinoma and papilloma of the urinary bladder by swabbing the lips and oral cavities of mice with cigarette tar residue. Kotin *et al.*, extracted carcinogenic hydrocarbons from cigarettes (80). A cigarette filter was ineffective in removing the carcinogen (79). Kotin *et al.* also demonstrated carcinogenic hydrocarbons in Diesel engine exhausts and related the high incidence of carcinoma of the lung to the greater air pollution in urban areas (80). Calculations were also made of the amount of arsenic and of 3,4-benzpyrene inhaled with polluted air during the life span of a "standard" man. The authors conclude that these amounts may be sufficient to account for the increased incidence of lung carcinoma (71). The "atmosphere" surrounding this topic is indeed highly charged with emotionalism and controversy, as discussed by Brues in his Presidential Address to the American Association for Cancer Research (81). The conclusion has been reached by several investigators that elimination of cigarette smoking would be the most important single preventive measure to check this alarming rise. While this suggestion meets resistance from tobacco-consumers and producers, reduction of air pollution, another important preventive measure, would certainly be welcomed by the general public.

While the rise in the incidence of lung cancer is regarded with considerable alarm, and the possible reasons for this increase are being investigated, what progress has been made in the treatment of lung cancer? Earlier diagnosis through mass chest x-ray surveys, reported from Los Angeles, Boston, and Philadelphia have not yielded the expected results; although a higher percentage of asymptomatic cases is resectable, the survival rates have hardly improved (82 to 84). The value of exfoliative cytology in studying sputa and bronchial aspirates is generally recognized. McCormack *et al.* reported 58 per cent positive results obtained from bronchial swabbings as against 26 per cent positive biopsies in 400 cases of proven cancer of the lung (85). A careful description of the preservation and staining of specimens, and of the morphologic appearance of cancer cells in sputa is contained in a recent report (86). The treatment of pulmonary neoplasm is surgical. The results obtainable with lobectomy are comparable to those of pneumonectomy (87). Other forms of treatment such as high voltage x-ray therapy, isotopes, and nitrogen mustard are being further explored (88 to 90). Although it is too early to appraise the results obtainable with megavolt radiotherapy, they appear to be superior to those of conventional radiotherapy (91). Berg *et al.* injected radioactive colloidal gold into the bronchial mucosa of animals and found that a significant amount of radioactivity was transported into and deposited within the hilar lymphnodes; the speed of this transport was such that the radiation of the lymphnodes was still sufficient. However, the distribution was patchy (89). Pochin *et al.*

injected radioactive colloidal gold intravenously into rabbits and intravenously or via cardiac catheterization into the pulmonary artery of man. Two patients with adenocarcinomatosis of the lung received a therapeutic dose. The isotope was well-retained in the lung; however, this procedure is in the early experimental stage (92). Nitrogen mustard injected intravenously has induced subjective and objective improvement in a few cases of small cell (oat cell) carcinoma of the lung (90).

Newer data on the treatment of bronchial adenoma have appeared. Soutter reports from the Massachussetts General Hospital that 38 of 43 patients treated with resection are living and well; 50 per cent of these patients had local invasion (93). Overholt reported that 44 of 48 patients are living and well after lobectomy or pneumonectomy; there were only two operative deaths (94). The prevailing opinion is that although bronchial adenomata rarely metastasize they are locally invasive, and surgical excision is the treatment of choice. Jackson, however, points out that half of his cases were treated successfully with bronchoscopic resection, and advocates thoracotomy only for those who can not be cured by the resectoscope (95).

Thyroid.—Some surgical centers advocate removal of all solitary thyroid nodules since a high percentage is malignant. This certainly applies to solitary nodules in individuals under 20 years of age, in whom 59 per cent may be malignant (96). However, there are only 138 such cases reported (97). It does not seem to apply to adults since single or multiple thyroid nodules are common, especially in goiter areas, whereas carcinoma of the thyroid is rare and accounts for only 0.7 per cent of all cancer deaths (98). Sokal reported only 70 cases of carcinoma of the thyroid among 400,000 admissions at the New Haven Hospital (99); 26 cases were reported per year, or 3.4 cases per 100,000 population, from San Francisco (100); only 301 cases were seen at Memorial Hospital in New York City in the period 1930 to 1946 (101). Miller reported from a large hospital in a goiter belt 32 cases of carcinoma of the thyroid in 10 years, and estimated that the incidence of malignancy in thyroid nodules is as low as 0.2 per cent (98). Crile's data from a thyroid center confirm the low incidence of carcinoma of the thyroid (102).

A geographic survey of 15 countries demonstrated the interesting relationships of iodine deficiency, increased incidence of goiter, and the occurrence of carcinoma of all sites (103). Simpson *et al.* (104) noted an increased incidence of thyroid carcinoma in patients who were previously treated with radiotherapy for thymic hyperplasia. Dailey *et al.* reported 38 patients with thyroid adenoma and 35 with papillary adenocarcinoma in a group of 205 patients with Hashimoto's disease (105). Papillary adenocarcinoma is a very slow-growing neoplasm and is most frequently encountered in the age group under 40 years, whereas undifferentiated thyroid tumors occur after middle age (102).

Of considerable interest is the development of I^{131} therapy for metastatic thyroid carcinoma. The first patient (106) was so treated at Montefiore Hospital in 1943 where a total of 125 patients were subsequently studied.

Only in a minority of cases of carcinoma of the thyroid do metastases take up sufficient radioiodine to warrant I^{131} therapy. Thyroid metastases which fail to concentrate this isotope may do so after the elimination of the competing thyroid gland by surgery or radiation (107). The uptake in metastases was sufficient and the follow-up period long enough in 16 patients to permit clinical evaluation; the majority of these patients showed subjective and objective improvement. However, two patients died with acute myelogenous leukemia, four and five years after the initiation of radioiodine therapy, and a possible relationship of the development of leukemia to ionizing radiation was considered (108). I^{131} is discharged more rapidly from the carcinomatous thyroid gland and from metastases than from normal thyroid tissue (109). By relating the percentage uptake and the biological half-life of I^{131}, a product was obtained which was helpful in diagnosing carcinoma of the thyroid (110, 111).

Head and Neck.—Better results are being reported in the treatment of tumors of the head and neck by both surgery and radiation, although the current trend seems to favor surgery. Modlin and Slaughter favor surgery. Modlin reports an over-all five-year cure rate of 47 per cent in 150 patients with carcinoma of the floor of the mouth (112). Even in advanced cases of intra-oral carcinoma, some of which were radiation failures, Slaughter reported a 32 per cent five-year cure with surgery (113). Ash & Millar (115), Lampe (114), and White *et al.* (116) favor radiotherapy and report good results. Ash reported on over 400 patients seen in 20 years who were treated with interstitial and external radiation; in early carcinoma of the tongue the five-year survival was 76 per cent, and in tumors of the floor of the mouth 73 per cent. White *et al.* emphasize that larger cancericidal doses delivered by improved methods of radiation will give better results although radiation necrosis of bone remains a hazard. It is generally agreed that local recurrence or regional lymphnode metastases are best treated surgically. Tumors of the nasal cavity and of the paranasal sinuses were treated at Radiumhemmet with radiation, excision, and lymphnode resection; 45 per cent of the cases survived five years as compared to only 9 per cent treated with radiation alone (117). Most sastisfactory results were obtained with radiotherapy for carcinoma of the larynx; 80 per cent in Stage I and 68 per cent in Stage II were free of disease five years later. However, in Stage III surgery was the treatment of choice, as 53 per cent survived five years contrasted to only 24 per cent treated with radiotherapy (118). It seems likely that the radiation results of patients in Stage III will improve; 60.4 per cent of patients with advanced carcinoma of the larynx treated with telecurie therapy, using 10 gm of radium as a radiation source, survived three years (119). It is of interest to note that the incidence of carcinoma of the larynx has remained unchanged in the past decades although the incidence of carcinoma of the lung has markedly increased (120).

Gastrointestinal tract.—The outlook for patients with gastrointestinal carcinoma is still poor. This is principally due to the fact that the diagnosis

is usually made late when the various regional lymph nodes are already involved and the veins are invaded. For instance, Astler & Coller found that in 82 per cent of 356 cases of carcinoma of the colon all layers were involved by tumor, and in 40 per cent the lymphnodes as well (121). Fisher & Turnbull (122) found tumor cells in the veins of 32 per cent of surgically resected specimens. Barringer *et al.* demonstrated roentgenographically areas of vein obstruction in resected specimens of carcinoma of the colon. When these sites were examined histologically tumor involvement was found (123).

While it is generally recognized that mass screening of the population is impracticable, the most thorough application of clinical and laboratory techniques to patients with vague symptoms may lead to early detection and improve the long-term results.

Encouraging results have been obtained by the use of exfoliative cytology in the study of malignant lesions of the esophagus, stomach, colon, and even pancreas (124, 125). The specific techniques used have been described. Data were presented which seem to indicate that the accuracy of this technique surpasses those of endoscopy and x-ray examination. In lesions of the esophagus the author claims an even greater accuracy for exfoliative cytology than for direct biopsy (125).

Improvement of the long-term results could be expected with early removal of polyps of the stomach, since a certain percentage are malignant and others are considered to be precancerous (126 to 128). Similar improvement could be expected with early surgery of gastric "ulcers" since 10 to 15 per cent of patients operated on for gastric ulcer had unsuspected carcinoma (129 to 131). This applies specifically to ulcers located on the greater curvature, between the angulus and pylorus, and to those which do not heal completely after medical therapy (132). A recent report from the Mayo Clinic, surveyed 226 cases of carcinoma of the stomach in which the lesions were less than 4 cm. in diameter. These patients had ulcer-like lesions. The correct diagnosis of cancer was made in only one-third of the patients. The lymphnode involvement by tumor was directly proportional to the size of the lesion; in lesions less than 1 cm. in diameter the incidence was 11 per cent and the five-year survival 82.4 per cent, while the five-year survival for the entire group was 31.6 per cent (133). These authors emphasize the resemblance of the clinical symptoms of this type of gastric carcinoma to benign ulcer: dyspepsia of several years duration, presence of free hydrochloric acid, and roentgenograms which are barely distinguishable from benign ulcer. The relationship of polyps and of ulcerative colitis to carcinoma of the colon has been well-documented by several studies; the incidence of malignancy is reported to increase with the duration of colitis (134 to 136).

Data on the results of surgical treatment of carcinoma of the esophagus are now available from three large clinical centers. Sweet (137) reports a series of 159 patients; the five-year survival of those with "operable" lesions

of the lower third of the esophagus was 34 per cent. Garlock & Klein (138) report on 457 patients with carcinoma of the lower third of the esophagus; 44 per cent were resectable and the five-year survival of these was 41 per cent. Carey & Clagett review 475 patients; 27 per cent were resectable and 32 per cent of these survived three years or longer (139).

The outlook for the patients with carcinoma of the stomach can be judged from the following statistics compiled at two large institutions: of 1200 patients with carcinoma of the stomach seen at New York Hospital in the past 20 years, the over-all salvage rate was 5 per cent in the first 10 years as compared to 8 per cent in the last decade (132). The corresponding figures from Pack's statistics are 4 per cent and 14 per cent respectively; however, he reports a 34.8 per cent salvage rate for patients with resectable lesions in the last decade (140). Several surgical groups advocate adequate resection of the tumor and total gastrectomy for selected cases only (141 to 143). However, it is true that the extent of the involvement of the stomach by tumor can be only inadequately judged by x-ray, gastroscopy, or even inspection, and the rate of recurrence of tumor in the stomach and duodenal stump following subtotal resection is high (144).

The over-all five-year survival rates of patients with carcinoma of the colon was 13.2 per cent in the State of Connecticut in 1935 and 21.3 per cent in 1949 (145); Hallstrand (146) reports a five-year survival of 25 per cent. Astler & Coller (121) note a five-year survival of 44 per cent after resection and 54 per cent for those without lymphnode involvement.

Recent investigations have re-emphasized the association between the socio-economic and nutritional factors and the incidence of gastrointestinal neoplasms; these studies may lead to new clues for experimental investigations. A 65 per cent incidence of chronic alcoholism was reported from Denmark in a series of patients with carcinoma of the esophagus (147). Kennaway re-emphasizes the strong association of carcinoma of the hypopharynx in females with the Plummer-Vinson syndrome which may precede the development of post-cricoid neoplasms by several years and may be prevented by early correction of the metabolic nutritional defect (120). An absolute decrease in the incidence of gastric carcinoma has been documented from the United States (148), and from England and Norway (149) in the past 20 years in spite of the increase of malignancies of all sites (150). This striking decrease continues and is apparently associated with improvement of the standards of living. A higher incidence is reported for the poorer class in England and Norway; also, a generally higher incidence is reported in rural than in urban areas although the over-all incidence of cancer is higher in cities (150, 151). In this country, Ivy associated this decrease of the mortality rate from stomach cancer with a change in food preparation. He quotes from cooking manuals in which lower temperatures are currently recommended and conjectures that one factor which may have contributed to this decline is less heating of dietary fats. This investigator was able to produce malignant tumors in rats by injecting heated fats and suspects that some of

the dyes approved for human consumption may also be low grade carcinogens (152).

Genito-urinary tract.—Little progress has been made in recent years in the diagnosis and treatment of tumors of the urinary tract. The difficulty in early diagnosis of renal carcinoma and the low salvage rate (153) stimulated the search for improved diagnostic tools. Exfoliative cytology has not allowed earlier diagnosis. New diagnostic methods such as nephrography (154), nephrotomography, and abdominal aortography (155) have been devised for the visualization of renal tumors and for their differentiation from other tumors of the retroperitoneal space (156).

Newer measures were introduced for the treatment of papillary carcinoma of the bladder; these were the introduction of inflated rubber balloons containing isotope solutions (157, 158) or of a Co^{60} point source (159) into the urinary bladder, and the use of Co^{60}-teletherapy (88). Radioactive yttrium solutions may find a place in the treatment of intravesical tumors since this isotope has a more favorable radiation spectrum and a suitable half-life (160, 161).

Recent data indicate that radical prostatectomy gives the best results in patients with carcinoma of the prostate; Scott (162), Colston (163), and Jewett (164) reported that 50 per cent of the patients survived five to 10 years. Some patients with local extension of the disease may become operable following estrogen therapy (165). However, the over-all operability rate is rather low even in large urological centers, e.g., 22.7 per cent, although it was reported to be much higher, 54.5 per cent, in one of the large army centers (163). Of all patients with carcinoma of the prostate 95 per cent had metastatic disease when first seen by a physician (162). Periodic examinations of prostatic smears for early diagnosis in asymptomatic patients have yielded unsatisfactory results (166, 167). Transurethral biopsy is not expected to disclose early malignancies since these are usually located in the posterior portion of the gland (168). Aspiration biopsies failed to discover tumor in 16 of 21 patients (169). However, a good diagnostic yield was obtained with this method by Colby (170). Periodic, open perineal biopsy, was advocated for early diagnosis (171, 172). Disagreement on the practicality of the latter approach has been expressed (170, 173). The serum acid phosphatase is normal in approximately one-third of the patients with advanced carcinoma of the prostate (174). Fishman *et al.*, confirmed by Day *et al.*, have shown that the "true prostatic" serum acid phosphatase was elevated in a number of such patients although the total serum acid phosphatase was within the normal range (175 to 177). Hudson *et al.*, using different techniques, came to similar conclusions (178 to 180).

The treatment of metastatic prostatic carcinoma by orchiectomy and estrogen therapy, introduced by Huggins, is the finest example of true palliation. Adrenalectomy has been advocated for patients in relapse. However, the long-range results obtained with this procedure seem to be rather disappointing (173, 181). Cortisone (medical adrenalectomy) and even

testosterone may give relief in an occasional case (173). Good palliative results have been obtained by the interstitial application of radioactive gold in moderately advanced cases of prostatic cancer without distant metastases (182). The effect of radioyttrium colloids in lieu of radiogold is being investigated; yttrium remains well-localized in the prostatic gland of animals (183).

Palliative therapy.—The progress in this field is most gratifying. The advances in hormonal therapy of carcinoma of the breast and prostate have already been commented upon in the respective sections. Chemotherapy, which barely existed a decade ago, has developed into one of the major experimental and clinical disciplines in the field of neoplastic diseases. The chemotherapy of the lymphomas and leukemias has been extensively reviewed and the reader is referred to several articles and monographs dealing with this subject (1, 184 to 193). The indications, contraindications, side reactions, and the results which can be expected from the use of these agents are described in detail in these reviews. Although palliation has been achieved, prolongation of life has been demonstrated only in the acute leukemia of children. Burchenal reports that 52 per cent of children with acute leukemia survive one year or longer when treated with amethopterin, cortisone, and 6-mercaptopurine, 29 per cent with cortisone and amethopterin, versus 5 per cent untreated controls (190). Favorable results were reported with myleran in the treatment of chronic myelogenous leukemia. This agent has been recently introduced by the Chester Beatty group (194 to 196). Chemotherapeutic palliation of solid tumors met with limited success; nitrogen mustard in the treatment of oat cell carcinoma of the lung (90), triethylenemelamine (TEM) for ovarian carcinoma (197), and nitrogen mustard, TEM, or urethane for nasopharyngeal carcinoma have achieved palliative results in cases beyond surgery and radiotherapy (198, 199). Combination therapy of urethane and TEM was used in 17 cases of multiple myeloma; significant palliation was reported without undesirable side effects (200). Radiotherapy and nitrogen mustard was very successful in the treatment of one case of choriocarcinoma; pulmonary metastases disappeared and did not recur for two years following therapy (201). Patients with advanced carcinoma of the ovary and breast, and those with melanoma were treated with triethylene thiophosphoramide (THIOTEPA) orally, intravenously, and intratumorally; it was also injected into body cavities for the treatment of malignant effusions. Reduction of tumor growth and fluid accumulation, as well as increased comfort, were reported in a fair percentage of patients so treated (202 to 205). Newer compounds are continuously being screened for tumor therapy. Sarcolysin, a substituted amino acid, is promising according to Russian authors since it inhibits markedly the growth of experimental tumors (206). Furst *et al.* screened 83 compounds structurally related to formamides in Ehrlich ascites tumor; N-methylformamide was found to be the most active (207). An antibiotic, stylomycin, had inhibitory activity against a variety of experimental tumors but showed

little activity when tested in 51 patients with advanced cancer of various types (208). The combination of radiotherapy and aureomycin injected intravenously, interstitially, or intraarterially in patients with advanced pelvic or intra-abdominal neoplasm was reported to give good palliative results; operation became possible in 15 of 39 such patients and nine of these had no evidence of disease four to nine months after therapy (209). Therapeutic effectiveness of an agent is not necessarily dependent on its selective concentration in tumor tissue as was demonstrated with radioactive TEM (210).

The palliative results obtained with ionizing radiation delivered by improved methods, as reviewed by Gellhorn & Holland (184) and by Haddow (1), have already been commented upon in this review. There are continuing efforts to enhance the effect of ionizing radiation by the use of sensitizing agents such as Vitamin K (211), Vitamin C-deficient diet (212), and increasing the oxygen tension of respiratory air (213, 214). The histo-pathologic changes subsequent to neutron capture therapy were studied in eight cases of glioblastoma multiforme. Viable tumor was found to persist in all cases; radiation effects were noted in the tumors of three patients (215). Reports on the effects of radioactive colloidal gold in the treatment of effusions due to malignancy continue to appear. In a patient with massive ascites due to mesothelioma that required 250 paracenteses in 18 months prior to treatment, excellent results were reported with radioactive gold (216). The intrathecal instillation of Au^{198} in conjunction with radiotherapy is suggested in patients with medulloblastoma (217). Because of the more favorable radiation characteristics, and the greater safety to patients and personnel, the therapeutic usefulness of $yttrium^{90}$, a beta-emitting isotope with a 64-hr. half-life, was further investigated. After extensive tracer studies in animals and in cancer patients showed good localization (218a, 218b, 219, 220), therapeutic doses of Y^{90} were administered intrapleurally or intraperitoneally and favorable results were obtained (221). Other uses of Y^{90} such as instillation into the urinary bladder, injection into the prostate, into the endometrium, and into the hypophysis are being explored (33, 160, 161, 183, 222, 223).

Pain and psychological aspects in cancer patients were discussed by Gellhorn & Holland (184) in the *Annual Review of Medicine* in 1954. It is genally assumed that cancer is accompanied by severe pain and analgesics are administered to most cancer patients. Approximately 300 such patients who had received analgesics for many weeks or months were studied at Montefiore Hospital. It was found that "pain" could be equally well-controlled by placebos in over 50 per cent of these patients (224). Chlorpromazine was advocated as a potentiator of analgesics (225), as an anti-emetic, and in the treatment of radiation sickness (226).

One of the most significant advances in palliative cancer therapy, namely improved medical care, is due to the increasing attention which cancer patients receive in hospitals and in private practice. The homes for incurables

are gradually disappearing, and the home care practice is extending medical care to the indigent cancer patients in their homes. The team of surgeons and radiotherapists is strengthened by the increasing participation of internists and general physicians. Their alertness to recognize and treat nonmalignant conditions in patients who have had or still have cancer greatly aids the management of cancer patients (227).

Laboratory Investigations

Carcinogenesis.[2]—The problem of carcinogenicity and chemical configuration continue to interest many investigators. The relationship between electronic structure and carcinogenicity, first studied by Schmidt (228), then by Pullman & Pullman (229), by Daudel (230), and others (231 to 233), has been further explored by Japanese investigators (234), and the significance of frontier electrons in chemical reactions of the π electron systems emphasized. A close correlation between carcinogenicity and frontier electron distribution was noted. This approach seems to be of theoretical and possibly also of practical interest for screening new compounds for their carcinogenicity. The Madison group continued to relate chemical configuration to the production of tumors of certain types, and studied compounds related to 2-acetylaminofluorene; the fluorene nucleus seems to be essential for the production of hepatoma, the tricyclic compounds for tumors of the epithelium of the small intestine and of the ear duct, and the biphenyl nucleus for tumors of the breast (235). The literature on the induction of tumors of the thyroid (236, 237) and of the pituitary (238) has been recently reviewed. Thyroid tumors were also produced with iodine-deficient diet alone and their induction was hastened by the addition of 2-acetyl-aminofluorene (239). Tumors of the stomach have been produced experimentally in rats by placing methylcholanthrene into the stomach wall (149, 240). Adenocarcinoma of the liver and hepatoma were produced in hamsters and mice with bile concentrates from patients with cancer of the common bile duct (241), indicating the presence of a carcinogenic substance in the bile of such patients. This reminds one of the chemical similarity of bile sterols and carcinogenic hydrocarbons as studied by Fieser. Tumors were produced by the implantation of methylcholanthrene into the gallbladder of cats (242). Derangements of tryptophan metabolism have been further investigated in animals and in man as one of the causes of carcinoma of the urinary bladder. The experiments of Dunning *et al.* (243) were confirmed by Boyland *et al.* (244) who produced carcinoma of the urinary bladder by feeding 2-acetylaminofluorene to rats maintained on a diet of hydrolyzed casein reenforced with tryptophan. These authors assume a summation of the carcinogenic effects of the chemical and the breakdown products of tryptophan excreted through the bladder. A separation of these tryptophan derivatives which are excreted in the urine of patients with carcinoma of the urinary bladder was carried out (245).

[2] See also the sections on carcinoma of lung and of the gastrointestinal tract.

The role of the pituitary gland in carcinogenesis was further investigated. Robertson *et al.* report that hypophysectomized rats were protected against carcinogenic action of the azo dyes; the carcinogeneity of these dyes was partially restored by adrenocorticotropin and pituitary growth hormone and to a lesser degree by thyrotrophin and gonadotrophin; pituitrin, cortisone and testosterone were ineffective (246). The induction of tumors by methylcholanthrene was also inhibited by hypophysectomy (247). On the other hand, Antopol *et al.* emphasized that the hypophysis is not essential for the induction of tumors with 3,4-benzpyrene (248). Bittner and his colleagues reported on a heat-stable substance, extractable with acetone or ether from transplanted tumors, which accelerated the take of mammary tumors and decreased the life span of the hosts pre-treated with this preparation (249, 250). The carcinogenicity of ionizing radiation was further studied in animals and man. Koletsky & Gustafson noted a high incidence of benign and malignant tumors in rats surviving an LD_{70} dose of total body radiation (251). Twenty-one new cases of malignant tumors which developed after a latency period of 4 to 40 years subsequent to x-ray treatment for nonmalignant conditions such as hemangioma, eczema, Graves' disease and others, were added to the approximately 200 cases already reported in the literature (252). The relationship between leukemia and ionizing radiation in animals and man has recently been reviewed by Kaplan (253). The incidence of leukemia was higher in patients who had received radiotherapy for arthritis or for thymic hyperplasia than in a comparable nonirradiated group (104, 254). The fate of the Japanese atomic bomb survivors was further followed; the incidence of leukemia seems to be receding from its previous peak and fewer new cases are being discovered; leukemia developed also among those who had no acute radiation signs such as burns or epilation at the time of the atomic blast (255, 256).

An interesting discovery was made on the mechanism of carcinogenesis by correlating cancer mortality with age; when both were plotted on a logarithmic scale a linear relationship was obtained, with the death rate increasing six to seven times more rapidly than the age (257, 258). While the relationship holds true for the overall death-rate from all malignant tumors, Armitage & Doll (259) noted important exceptions for certain types of neoplasms, namely, carcinoma of the lung, bladder, and prostate in males, and lung, breast, ovary, cervix and corpus uteri in females. These exceptions indicate the dependence of tumors of such sites on enhancing factors, e.g., hormonal or environmental. The development of a cancer cell is assumed to be the end result of six to seven cell mutations. The known long latency between exposure to the carcinogen and the development of tumors in animals and in man is in accordance with this theory of multi-mutations (259). Iversen, however, favors a single hit mechanism (260).

The experimental data which favor virus etiology of malignant tumors have been recently summarized by Oberling & Guérin (261). Gross believes that a group of submicroscopic oncogenic agents is transmitted through the

germinal cells to the progeny of chicken, mice, cattle, and possibly man. These agents may remain latent throughout the life span of the carrier host, but may occasionally, triggered by intrinsic or extrinsic stimuli, cause rapid cell multiplication leading either to the development of leukemia or other malignant tumors (262). This investigator was able to transmit leukemia into new-born nonleukemic strains of mice of the AK or C57 inbred lines. Some of the inoculated mice did not develop leukemia but bilateral parotid gland tumors (263). MacDowell found an agent in old mice of a certain strain which reduces the incidence of leukemia and significantly prolongs the life-span of a highly susceptible strain of mice. This agent is transmitted to progeny through the placenta or milk (264).

Immunology.—The trends in immunologic research have been reviewed by Hauschka (265). One aspect of the tumor cell in the tumor-host relationship was investigated by Hauschka and by Kaziwara (266) and further evidence was presented that the antigenicity of the tumor transplants depended on the number of chromosomes of the transplanted cells. The importance of the host was emphasized in the studies of Strong (267) and of Cohn & Zimmerman; they were able to demonstrate the effect of the environment upon the microscopic structure of the tumor. A mouse ependymoma transplanted into the allantoic membrane of chick embryo grew into loose clusters of glial tumor cells which, however, grew into ependymoma again upon subsequent transplantation into mice (268). The original transplant seems to retain its immunologic properties, e.g., human tumors grown for many generations in rats, hamsters, and in allantoid membranes retain their original human antigen (269a). Antibodies against certain tumors have been occasionally demonstrated; however, they were not strictly specific for the tumor antigen (269b to 271). Antisera agglutinated suspensions of melanin granules strongly and specifically although no specific localization of anti-melanin gamma globulin—tagged with I^{131}—occurred in melanoma (272). Adelsberger & Zimmerman continued their study on the reactions of erythrocytes in tumor-bearing mice (273). In contrast to the marked hemolysis of red blood cells of nontumor-bearing C_3H mice, inhibition of hemolysis was observed in the early or moderately advanced stages of a well-growing tumor transplant. They assume, on the basis of other experiments (274), that the erythrocytes of C_3H mice bearing tumors carry an antibody which inhibits hemolysis and acts best in the early stages of tumor growth. Similar findings have recently been reported by Ponder & Ponder (275). They were able to demonstrate, on the red blood cells of tumor bearing mice, antibodies or substances reacting like antibodies by either the Coomb's method or elution technique, or both. There has been extensive investigation of the role of immune iso- and heteroagglutinins following transplantation; a rise in agglutinin titer was noted not only after tumor transplantation but also after grafts of normal skin or of other normal tissues. This topic was discussed in a recent symposium (276). The role of hemagglutinins in relation to tumor growth and tumor immunity has been extensively studied by Nungester

& Fischer (277). A rabbit antiserum was prepared against pellet fractions of mouse lymphosarcoma; it agglutinated mouse red blood cells and provided protection against mouse lymphosarcoma when the serum was injected undiluted within 96 hr. after transplantation. These authors were able to remove the agglutination factor by absorbing the antisera to mouse red blood cells without interfering with the protective properties of the serum against the tumor. The resistance of mice to multiple inoculations of a transplantable tumor was studied by Barrett & Hansen. In the presence of a natural or induced immunity of the host, inoculations failed. Some of the animals in which the transplant grew were thereby rendered immune to further inoculation. This immunity was lost when the tumor reached a larger size; loss of immunity was explained on the basis of general deterioration of the host (278). Inoculation into the eye or brain of mice provided less immunity to subsequent inoculations than inoculation into other tissues of the animal, indicating a relative isolation of these sites from the host body (279). Graham & Graham tested sera of 46 gynecological patients for the presence of antibodies to their own tumors by the complement fixation technique; 12 of these patients showed significant antibody titers. Most of the negative tests were in patients with far-advanced disease (280). A serological flocculation test for malignancy has been employed in over 6000 patients, using spleen extracts obtained from patients with generalized carcinomatosis as the antigen. The results so far indicate lack of specificity (281). Three other serological screening tests have been evaluated by Sprunt *et al.* and were found to be unsatisfactory (37).

Hematology.—The anemia of cancer patients was further investigated. As was previously pointed out anemia is only rarely due to replacement of bone marrow by tumor, depression of erythropoiesis, defective composition of the red cells or of hemoglobin (184, 282). It was shown that the survival time of red cells of normal donors was significantly shortened when transfused to patients with malignancies (282 to 285). However, the survival time of red cells of cancer patients was within the normal range when transfused to normal volunteers. These experiments suggest the presence of a plasma factor which may be responsible for the increased rate of red cell destruction and in part, for the anemia of cancer patients (286, 287). The increased bleeding tendency in patients with advanced carcinoma of the prostate, attributed to increased circulating fibrinolysins (288), was reported to be successfully treated with cortisone or adrenocorticotropin (289).

Bone marrow aspirations are important to assess the spread of malignancy to the skeleton. The superiority of iliac over sternal marrow aspiration for the recovery of malignant cells has previously been demonstrated in this laboratory (290). Bone marrow aspiration is indeed advocated as part of the preoperative evaluation of the patient since it may be positive when x-rays are still negative (291).

Data on preleukemic hematologic changes in man are very scanty; an absolute increase of basophilic cells and a decrease of the alkaline phos-

phatase content of leucocytes were noted in the Japanese atom bomb survivors who subsequently developed leukemia. The bone marrow aspirate showed a nonspecific picture in this prodromal stage (255, 256, 292). Block *et al.* studied the peripheral blood and bone marrow aspirates of patients in the preleukemic phase and noted abnormalities which differed in various patients and were not similar to those seen in the preleukemic phase of the Japanese (293).

Biochemistry.—Greenstein's "*Biochemistry of Cancer*" contains extensive information on the subject (294). Greenberg summarized the results of isotopic tracer studies of the biochemistry of cancer (295). The biochemistry of human cancer has been reviewed by Lemon *et al.* (296). The metabolic aspects were reviewed by Mider (297) and by Gellhorn & Holland (184). Attempts to detect qualitative biochemical differences between normal and tumor cells have failed so far. However, numerous instances of quantitative differences have been discovered, and upon these the foundation of chemotherapy is being laid. For instance, Shapiro *et al.* utilized such quantitative biochemical differences for cancer chemotherapy and described several tumor-inhibiting compounds (298 to 300). "The biochemical properties of cancer cells surpassing normal "are listed in Table 2 of an article by Lemon *et al.* (296). The separation of acid phosphatase of prostatic origin from the total serum acid phosphatase has been commented upon in the section on prostatic carcinoma (175 to 177). The changes in serum alkaline phosphatase as an indicator of tumor activity of the skeleton will be discussed in the section on calcium metabolism (301 to 303). Bodansky *et al.* re-emphasized that the elevation of serum alkaline phosphatase is one of the most sensitive indicators of hepatic metastases (304); this was confirmed in our laboratory in 170 cases (305). The elevation of serum aldolase in rats bearing carcinoma was discovered by Warburg (306), and confirmed in a recent study by Sibley *et al.* (307) who presented evidence that the source of this enzyme is the tumor rather than muscle as was assumed by Warburg. Changes in the composition of plasma proteins in man and in animals bearing tumor continued to attract considerable attention (308, 309). A marked rise of α-globulin and a decrease of albumin was noted in mice bearing Sarcoma 180 as early as a few days after inoculation when the transplant was barely palpable. Implantation of non-neoplastic tissues such as embryonic tissue, liver, and other tissues failed to induce these protein changes (310). Johnson *et al.* reported a decrease in γ-globulin in C_3H mice bearing spontaneous or transplanted tumor, and relate this decrease to depressed antibody formation and hence to a lessened resistance to carcinoma growth (311). Jirgensons analyzed the physical-chemical properties of purified serum albumin fractions obtained from cancer patients. No differences in the sedimentation, viscosity, and electrophoretic mobility were noted in sera of normal and of cancer patients. However, the optical rotation of the albumin solutions was abnormally low in 90 per cent of 115 sera of cancer patients (312). The plasma protein abnormalities of patients with multiple myeloma were

actively studied by several investigators. At Montefiore and Mount Sinai Hospitals in New York City, the sera of 91 myeloma patients were studied by the Tiselius technique and the majority of these patients had an abnormal γ-globulin pattern (313). The physical-chemical properties of this purified γ-globulin (314), and of cryoglobulin, have recently been reported (315). Sachs *et al.* found an abnormal lipid-like material and a carbohydrate associated with the abnormal myeloma protein; the total polysaccharides and glucosamines were markedly increased (316). These authors suggest that the abnormal carbohydrate may be in some way related to the deposition of para-amyloid in multiple myeloma. Osserman & Lawlor found protein abnormalities in serum or urine by electrophoresis in each case of myeloma. The carbohydrate anomaly discovered by Sachs *et al.* in plasma was not found in the urine; it is assumed that the carbohydrate is split off from the globulin moiety by an enzyme in the kidney and that the abnormal urinary protein is only a fraction of the larger molecule (317a, 317b). Lewis & Page (318) found by ultracentrifugation lower than normal values for $-S_{25-40}$ (β_1-lipoprotein) and for $-S_{1-10}$ (α_1-lipoprotein). The increased susceptibility of patients with multiple myeloma to infections, especially to recurrent attacks of pneumonitis, was further investigated and correlated with an absence or deficiency of immune globulin production. In this respect patients with multiple myeloma behave like those with agammaglobulinemia (319, 320).

Metabolism.—Metabolic aspects have been extensively studied in the past years at the cellular and tissue level and in intact animals. These investigations illustrate well the application of modern analytical tools to cancer research. Determinations of nucleoproteins of the cytoplasm and of the nucleus by direct microspectrophotometry (321, 322), the fractionation of cellular components by differential centrifugation (323), the use of radioactive tracers in the study of protein, nucleoprotein, and mineral metabolism (295, 324, 325) are some examples.

(*a*) *Protein metabolism.*—Newer data on protein metabolism in cancer based largely on the experimental work of his own group, were reviewed by Mider (297). Gellhorn & Holland extended this review and directed attention to the metabolic interrelation between the needs of the growing tumor and those of the host (184). It was shown that the tumor seems to be able to accept protein directly from the host without prior breakdown to free amino acids (326). However, it was also shown that the tumor tissue does not represent a complete nitrogen "trap" although a rapidly growing anaplastic tumor seems to approximate it (326, 327). Measurements of nitrogen balances indicate that nitrogen equilibrium and even retention can occur in patients with advanced cancer if the caloric intake is adequate and essential amino acids and growth factors are provided (328, 329). Although these balance studies do not differentiate the nitrogen retained by the growing tumor from that of normal tissue, the magnitude of retention indicates that it is not due to active tumor growth

alone. Elman *et al.* reported that positive nitrogen balances and increase of body weight, plasma proteins, and hemoglobin were observed following tube feeding of adequate nutrients to patients with advanced cancer and severe anorexia (330). The ability of cancer patients to adapt to extreme restrictions of protein intake is seemingly as efficient as in normals (331). However, if adequate nutrition is not feasible because of anorexia, and if the requirements of the growing tumor and of the host are not met, breakdown of normal tissue will occur in spite of maximal adaptation. Hyperlipemia, indicating rapid mobilization of fat depots to provide fuel, has been repeatedly noted in tumor-bearing animals and in cancer patients (297, 332 to 334). Attempts have been made to distinguish by metabolic balance experiments the protein gain or loss of the tumor from that of the host. Since the ratio of N:K and of N:P in tumor protein differs from that of normal tissue, this difference was utilized to measure the amount of tumor tissue formed or destroyed in a given period of time. This approach met with some success in cases of malignant lymphoma in which tumor rich in nucleoproteins was rapidly destroyed by nitrogen mustard (335), adrenocorticotropin or cortisone (336). The destruction of tumor tissue in patients with malignant lymphoma treated with ionizing radiation led to a marked elevation of uric acid excretion which was far in excess of the increase of urinary nitrogen excretion (331).

(*b*) Body composition and nutrition.—Another investigative approach to measure tumor growth and destruction in man was recently reported from this laboratory; the body composition and the body fluid compartments of patients with malignant lymphoma were measured before, during, and after radiotherapy. Metabolic balance techniques were employed in combination with isotopic techniques. It was noted that with the clinical improvement following radiotherapy there occurred a marked decrease of the lean body mass and of the intracellular fluid compartment and this was thought to be principally due to tumor destruction. The extracellular fluid compartment expanded in the phase of cell destruction (337).

Cachexia occurs usually in the late stages of neoplastic disease whereas clinical manifestations of vitamin deficiency such as severe atrophic glossitis and cheilosis are observed in the earlier stages; scurvy, pellagra, and neuropathies are infrequent (338). Peripheral neuropathies have been observed as the first clinical manifestation of multiple myeloma (338). A study of correlation between clinical and histopathologic changes of the oral mucosa, principally of the tongue of depleted cancer patients, has been reported from this laboratory (339).

(*c*) Calcium metabolism.—Calcium metabolism is of interest to the oncologist because the release of calcium caused by tumor in the skeleton may provide an index of tumor growth and of the effect of therapy. This subject has been recently reviewed by Gellhorn & Holland (184).

The high incidence of spontaneous or hormonally-induced hypercalcemia together with its mechanism and therapy have been discussed (340 to 342). The successful treatment of hypercalcemia depends on the inhibition of tumor growth in the bone. The calcium binding agent ethylenedi-

aminetetraacetic acid, Na-EDTA, has been used in acute hypercalcemic crises to lower the elevated serum calcium temporarily (343 to 345).

The relationship between serum calcium and alkaline phosphatase levels was studied in 36 breast cancer patients with bone metastases. An inverse relationship between the changes of enzyme content and of serum calcium was noted; the alkaline phosphatase declined when the serum calcium rose to hypercalcemic levels. A decline of serum alkaline phosphatase preceded hypercalcemia in several instances. Repeated determinations of alkaline phosphatase may therefore aid in the recognition of impending hypercalcemia (301). The negative calcium balances principally due to high urinary calcium excretion in patients with rapidly growing metastatic tumor in bone, the spontaneous fluctuations of calcium metabolism reflecting the fluctuant clinical course of metastatic breast carcinoma, and the improvement of calcium balance following hormonal therapy and castration (surgical or radiation) have been reported (303, 328, 342). Pearson *et al.* believe that spontaneous fluctuations of the urinary calcium excretion and increments of calciuria following estrogen administration indicate that the growth of such tumors is regulated by and dependent on estrogen levels. They also suggest that such estrogen-dependent tumors respond best to the removal of the endogenous sources of estrogen, the ovaries, and adrenals (29). Negative calcium balances and hypercalcemia occur in disseminated osteolytic lesions of all types including malignant lymphomas (328, 338). In disseminated osteoblastic metastases such as occur in prostatic carcinoma the pattern of calcium metabolism is quite different; in spite of widespread skeletal involvement the calcium balances may be normal, the urinary calcium excretion exceedingly low, and at times barely measurable (328, 346). Successful hormonal or castration therapy improves the calcium balances of patients with osteolytic or osteoblastic lesions. The decrease in calciuria which may occur within a few days of institution of therapy is a good prognostic sign. A simple test was reported from this laboratory for the study of calcium metabolism. The daily urinary calcium excretion was measured before and on the day of a 4-hr. infusion of 50 ml. calcium gluconate, and the excess calciuria and the calcium retention were calculated. In patients with predominantly osteolytic metastases the urinary calcium excretion may be high and the retention of the infused calcium low, while in predominantly osteoblastic metastases the reverse was noted. This calcium tolerance test was also found to be useful in evaluating the effect of therapy (325, 347 to 349). A correlation was noted between urinary calcium excretion and patient survival in multiple myeloma; patients with a urinary calcium excretion of 150 mg. or less per day had a much longer survival than those with hypercalciuria and hypercalcemia (338).

Conclusion

When one has concluded an annual review on neoplastic diseases and surveyed the vast amount of research conducted in this field, one is tempted to draw conclusions and to predict trends for the future. The essential clues

are still missing, and qualitative differences between malignant and normal cells are still undiscovered. The real progress seems to lie in bringing into focus the study of malignant tumors in man. It has enlightened us on environmental factors involved in the development of cancer, and it has clarified the long latent period of preinvasive stages during which curative treatment can be applied with greatest success. The advances in surgery, the development of ingenious tools to deliver ionizing radiation, the rapid growth of the new discipline of chemotherapy augur well for the future and promise benefits to an increasing number of cancer patients.

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IMMUNITY[1]

(Properdin, Agammaglobulinemia, Irradiation and Immunologic Paralysis)

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The plaint is sometimes made that our understanding of immunologic processes has come very little beyond the stage at which it was left by the founding fathers. The variety of very stimulating recent advances in comprehension of aspects of native resistance and of various features of acquired immunity refute this viewpoint, though it is true that in many instances we find the skeletons of these advances created, and sometimes lightly clothed in evidence, in the literature of 50 or more years ago. But the fact remains that what were intellectual exercises have in some cases approached becoming proved facts, and what were bare facts have been shown to have broad general application. This has frequently come about, furthermore, in a most stimulating fashion, through a combination of applications of fundamental cellular, chemical, and serologic studies with astute clinical observation and experiment. A case in point is the contributions of studies, employing marked antigens and antibodies, x-radiation, tissue culture and human cases of agammaglobulinemia, to the story of mechanisms of acquired resistance to infection. An analogous concatenation of investigations has broadened our knowledge of the processes of native resistance, and it is with aspects of these two main questions that this review is concerned.

NATIVE RESISTANCE TO INFECTION

Chemical Factors in Blood and Tissues

Since Nuttall's (1), Buchner's (2, 3) and, more recently, Mackie & Finkelstein's (4) summaries of the inhibitory activities of the blood of presumably normal animals upon bacteria, a number of substances with antibacterial or antiviral properties have been characterized. The earliest well-known one was Fleming's lysozyme (5), a mucolytic enzyme with activity on a variety of Gram positive bacteria, and with a wide distribution in body fluids and tissues consonant with the concept that this substance contributes to the ability of the normal body to discourage the growth of microbes on and in the tissues. More recently, another characterizable substance has been found to have an effect upon anthrax bacilli (6) and other organisms (7); this, like lysozyme, is a basic polypeptide. An oxidative deamination product of polyamine tissue derivatives called spermine and spermidine has been shown to kill tubercle bacilli (8). These basic substances appear to con-

[1] The survey of literature pertaining to this review was completed in August, 1955.

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IMMUNITY[1]

(Properdin, Agammaglobulinemia, Irradiation and Immunologic Paralysis)

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The plaint is sometimes made that our understanding of immunologic processes has come very little beyond the stage at which it was left by the founding fathers. The variety of very stimulating recent advances in comprehension of aspects of native resistance and of various features of acquired immunity refute this viewpoint, though it is true that in many instances we find the skeletons of these advances created, and sometimes lightly clothed in evidence, in the literature of 50 or more years ago. But the fact remains that what were intellectual exercises have in some cases approached becoming proved facts, and what were bare facts have been shown to have broad general application. This has frequently come about, furthermore, in a most stimulating fashion, through a combination of applications of fundamental cellular, chemical, and serologic studies with astute clinical observation and experiment. A case in point is the contributions of studies, employing marked antigens and antibodies, x-radiation, tissue culture and human cases of agammaglobulinemia, to the story of mechanisms of acquired resistance to infection. An analogous concatenation of investigations has broadened our knowledge of the processes of native resistance, and it is with aspects of these two main questions that this review is concerned.

NATIVE RESISTANCE TO INFECTION

Chemical Factors in Blood and Tissues

Since Nuttall's (1), Buchner's (2, 3) and, more recently, Mackie & Finkelstein's (4) summaries of the inhibitory activities of the blood of presumably normal animals upon bacteria, a number of substances with antibacterial or antiviral properties have been characterized. The earliest well-known one was Fleming's lysozyme (5), a mucolytic enzyme with activity on a variety of Gram positive bacteria, and with a wide distribution in body fluids and tissues consonant with the concept that this substance contributes to the ability of the normal body to discourage the growth of microbes on and in the tissues. More recently, another characterizable substance has been found to have an effect upon anthrax bacilli (6) and other organisms (7); this, like lysozyme, is a basic polypeptide. An oxidative deamination product of polyamine tissue derivatives called spermine and spermidine has been shown to kill tubercle bacilli (8). These basic substances appear to con-

[1] The survey of literature pertaining to this review was completed in August, 1955.

stitute a family of potentially antibacterial substances available to the normal animal body. Recently, Tomcsik & Guex-Holzer (9) found that various proteins combine with bacterial surfaces at a pH between the isoelectric point of the protein and that of the cell surface, on the acid side of the former and the alkaline side of the latter. Basic proteins therefore combine at relatively high pH, e.g., lysozyme at 7.0 and protamine at 8.0. With organisms of the genus *Bacillus* as experimental model, it was shown that the capsular swelling demonstrable with specific anticapsular antibody at neutral pH could be duplicated by normal serum constituents at pH 4.4. Protamine, on the other hand, acted upon the cell wall and eventually caused bacillary disintegration at a pH above neutrality. Tomcsik (10) believes that basic substances appearing in inflammatory exudates may act in this manner *in vivo*, and illustrates this suggestion with peritoneal exudates of mice inoculated with the anthrax bacillus. It is interesting in this connection that a group of the antibiotics including tyrothricin, gramicidin, bacitracin, the polymixins, neomycin, and viomycin are all polypeptides and all highly effective as antimicrobial agents, though toxic for tissues [Regna (11)]. Certain of these at least are surface active agents altering the physical structure of the cell [Umbreit (12)].

Against the viruses also there appear to be normal tissue suppressive substances [Raffel (13)], though in general these have been defined in terms of activity and not of chemical nature.

One might think that this variety of indigenous "antiseptics," along with the important phagocytic activities of granulocytes and macrophages, could adequately explain the pattern of resistance of the nonimmunized body to casual infection by microbes of the environment. Recently, however, announcement was made of an additional protective device in the form of a normal constituent of plasma called properdin; this is of especial interest because of the apparent catholicity of its antimicrobial activities, and also because it may supply an answer to the confusing question of relationship of serum complement to the native bactericidal properties of blood. In the past, it has been frequently described [Mackie & Finkelstein (4); Osborne (14); Adler (15)] that the abilities of sera from various nonimmunized subjects to suppress bacterial growth or viability often depend upon a heat-labile property which is presumably complement. If this is so, then one infers the involvement of antibodies in this normal antibacterial mechanism, and once antibodies enter the scene there arises immediately the question of normality of the test subject with respect to some previous inapparent experience with the microbe in question (13). Academic though these considerations may appear, they are important to an eventual understanding of what constitutes true innate resistance, and by extension, how this is interfered with under such circumstances, for example, as irradiation injury.

The discovery of properdin may perhaps resolve these questions. Pillemer and his colleagues (16) describe this substance as a heat-labile euglobulin of

molecular weight of about 1,200,000, present in normal human serum to the extent of 0.03 per cent of total proteins, but absent from spinal, ascitic, and pleural fluids, colostrum, milk, and extracts of leucocytes and platelets. In serum it unites with a substrate—for example, a bacterium or virus—nonspecifically in the serologic sense, and to this combination one component of complement (C'3) may become fixed to exert a lytic or lethal action. (For this reaction, magnesium ion and other serum constituents also appear to be necessary.) Removal of properdin from normal human serum resulted in a loss of bactericidal properties for *Shigella dysenteriae*, *Pseudomonas*, and *Proteus* [Wardlaw *et al.* (17)] and of viricidal properties; these could be restored by readdition of properdin. A role of properdin in the antihemagglutinative—and probably antiviral—activity of normal human serum is also described. Bringing this study closer to conditions in nature, Pillemer & Ross (18) have demonstrated that zymosan, a constituent of yeast which has been employed throughout these studies for manipulation of properdin in serum because of its ready reactivity with this substance, rapidly lowers the blood level of properdin on injection into mice. This initial decline is followed, after two to 14 days, by a marked increase to above normal levels. Rowley (19) has found that the susceptibility of mice to *Escherichia coli* varies greatly, depending upon treatment with cell wall constituents which similarly influence the properdin level of the blood. During the first half-hour after injection of such material, mice become very susceptible to an ordinarily avirulent strain, but two days later, when properdin has returned to above normal concentrations, they become resistant even to strains which are ordinarily virulent for mice. Pillemer & Ross (18) quote Rowley further to the effect that the same variations in susceptibility follow injections of zymosan, and the cell walls of many bacteria as well as high molecular weight polysaccharides have the same effect (20).

Thus, the failure of complement-depleted sera to display the limited but undoubtedly important range of anti-infectious activity of normal blood may be due not to a lack of complement for activity in an acquired antibody reactive system, but to depletion of properdin as well as to the removal of a component of complement required for properdin activity.

In addition there are undoubtedly instances in which complement acts with so-called "normal" antibody to effect destruction of bacteria, especially in the case of Gram negative bacilli, as described by Mackie & Finkelstein (4) and Adler (15). As mentioned before, these may well be antibodies acquired through exposure to agents which have antigens in common with the bacterium under test, or there may actually exist such an entity as "normal" antibody consisting of globulin molecules fortuitously constructed so as to react with antigens which happen to be present in certain bacteria [Raffel (13)].

Agammaglobulinemia

Sources of evidence bearing upon the question of native resistance to infection, as well as upon the questions of origin of gamma globulins, anti-

bodies and the nature of acquired immunity to disease, are embodied in the recently described syndrome of agammaglobulinemia. A case reported by Bruton in 1952 (21) was that of a young boy who, during the last four years of his life, had 18 serious infections, chiefly bacterial respiratory disease. He failed to respond immunologically to pneumococcal antigens and to attempted immunization with diphtheria toxoid and typhoid vaccine, nor did he develop the usual antibodies after recovery from mumps, which he had on three occasions. Electrophoretic studies revealed the complete absence from his serum of gamma globulin, a constituent which normally accounts for about 15 per cent of total proteins. Since this report there has been a rapid accumulation of additional cases; two by Bruton and collaborators in 1952 (22), nine by Janeway and associates in 1953 (23), and others by investigators in this country and abroad (24 to 29). In a number of instances very low levels of gamma globulin in infants have been held responsible for sudden deaths from acute respiratory inflammations (30).

Bruton (21) and Prasad & Koza (31) have defined this syndrome as one in which there is very low or absent gamma globulin with total serum proteins within the normal range; a history of recurrent bacterial infections; an absence of isohemagglutinins and of the potentiality to acquire antibodies; and a favorable response to repeated injections of gamma globulin. This description, however, does not encompass all cases; as might be expected, variants occur in which gamma globulin is low or absent and is often accompanied by immunologic impairment, but which differ from those described. Thus, Schick & Greenbaum (32) 10 years ago described a 12-year-old girl with edema of hypoproteinemia and absent gamma globulin; Fried & Henley (33) have classified cases into those with edema and hypoproteinemia which respond to high protein feedings, and those of the kind already described. Good & Varco (29) point out that in these various disorders, gamma globulin depression is associated with disturbances of other plasma proteins, while agammaglobulinemia is a more specific failure of protein anabolism.

The "classical" form of agammaglobulinemia may be congenital or acquired. Janeway *et al.* (23) were struck by the occurrence of the disease in young males and suggested that it may be inherited through a recessive sex-linked gene. It is interesting in this connection that in Good & Varco's report (29) of six cases of congenital disease in males, there were two pairs of siblings represented.

The occurrence of acquired disease in adults is supported by cases in which the onset of repeated infections begins during adult life (28, 29, 31, 34, 35). It is not possible at present—nor perhaps will it ever be—to categorize the congenital cases as distinct from the acquired on the basis of concomitant characteristic changes in blood cellular picture or other histopathologic differences. Marked and variable hematologic changes accompany this disease; leucocytic patterns have been described as including persistent neutropenia (29), recurrent neutropenia (29, 36), leucocytosis (29), lymphopenia (37), and, more frequently, normal or somewhat high levels of lymphocytes (29).

Taken as a whole, the most striking cellular distinction common to cases of acquired as well as congenital agammaglobulinemia appears to be the absence of plasma cells in inflammatory exudates, bone marrow, and lymph nodes. Zinneman *et al.* (38) found a scarcity of plasma cells in these patients, and Good (39), and Good & Varco (29, 40), after an extensive study of cytologic changes, concluded that the agammaglobulinemic individual shows the sparsity of plasma cells not only under "ordinary" conditions, but also following intensive vaccination with bacterial vaccine, a procedure which in normal children resulted in a significant increase of these cells in the marrow and in the lymph nodes draining the area of vaccine injection. The latter authors believe that the disease is accompanied by malfunction of the reticulum, from which they think the plasma cells are derived. In view of the absence of gamma globulin and antibodies in these patients, and the repeated observations in experimental animals of the probable role of plasma cells in antibody manufacture, studies of this kind are obviously of utmost importance to the clarification of this matter.

The observations so far described raise a number of interesting points. The first concerns the basis for the recurrent bacterial (and occasionally viral) infections in these patients. In infants and young children especially, where opportunities for spontaneous immunization to environmental agents have presumably been few, can susceptibility to repeated infections be laid entirely to failure of antibody responses to inapparent as well as overt infections, or are processes of native immunity also impaired? A priori it would seem more logical that susceptibility is directly related to the obvious defect encountered: that concerned with antibody manufacture. Yet the variety of infectious agents to which these individuals are subject leads one to suspect that innate resistance may also be impaired, for it is difficult to believe that we all depend upon an array of acquired immunities for our day to day protection against the multitude of microbes in the environment. In the nature of immunologic events there can be no unassailable evidence to support this viewpoint; it would be virtually impossible to ascertain to what variety of potentially infectious agents an individual may have acquired humoral immunity not only through exposures to the agents themselves, but through stimulation by closely related antigens contained in some other biologic envelope. On the other hand, this knotty problem might be partly resolved through another approach: an inquiry into the possibility that in agammaglobulinemic patients there may be, in addition to failure of antibody synthesis, failure also of formation and function of the native nonantibody protective substances described earlier. This would include studies of the functional activities of blood leucocytes, and the presence in plasma of the various anti-infectious substances about which we have some knowledge. The reviewer is so far aware of only two studies of this kind, both concerned with properdin. Recently Wardlaw *et al.* (41) reported verbally, during a discussion of the properdin system in human serum, that agammaglobulinemic patients may possess lower than normal quantities of this anti-infectious substance, though in different amounts depending upon whether

the disease is of the congenital or acquired type. Pillemer[2] states that he has seen "little or no decrease in the properdin titers in agammaglobulinemic patients. Certain samples of serum, at times, show a very low properdin titer, but we are not always sure that this might not have been due to an infection [existing] when the serum was drawn." In a study by Skahen, Fien & Kirsch (42) of a young adult male with agammaglobulinemia (presumably congenital) and hospitalized because of cervical adenitis of unidentified etiology, properdin was found to be entirely lacking from the plasma. More studies of this kind might be edifying, as would determinations of levels of lysozyme and those other antimicrobial substances described earlier.

A second interesting point concerns the nature of acquired immunity to viruses. There exists some evidence (13) that alterations in cellular environment may create a milieu untenable for the propagation of certain viruses. In the case of some of these agents at least, acquired immunity may depend upon altered cellular conditions rather than upon the acquisition of antibodies which, though produced, could be merely adventitious byproducts resulting from the presence of foreign substances in the body. The existence of patients who are unable to form antibodies might eventually go far toward answering this question.

In dealing with this issue, the focal point is not whether children or adults fall prey to virus diseases, since the population as a whole is generally susceptible to certain of these in any case, in apparent or inapparent form. The main point here is how well the disease is handled, i.e., terminated, once it is under way, for presumably the acquisition of immunity has a large part to play in this; and perhaps more important, how frequently reinfections occur, especially in those diseases of childhood to which re-exposures are common but in which second attacks are rare. Some evidence is already at hand on this point, pro and con.

Against the viewpoint that acquired immunity to virus diseases in agammaglobulinemic patients shows differences from that to bacteria are the following reports. The original patient observed by Bruton (21) had recurrent mumps, and developed no antibodies against this virus. A cause and effect relationship certainly suggests itself here. Keidan *et al.* (43) reported the death of an eight-week-old girl from generalized vaccinia following vaccination; in this instance, however, it is surprising that sufficient maternal globulin was not still present to thwart the process, if lack of antibody accounted for the disease; furthermore, administration of gamma globulin failed to halt the disease. It seems very probable that factors other than the failure of this infant to produce antiviral antibodies were responsible for the outcome. Good & Varco (29) report in one of their seven cases (a six-year-old boy) the occurrence of a mild generalized vaccinia following vaccination, in this case, however, with rapid recovery.

Opposed to these isolated observations suggesting the importance of the

[2] Personal communication to the author, October, 1955.

antibody-producing capacity to the ability to cope with virus infections stands the impressive fact that most observers of agammaglobulinemia have failed to note any remarkable frequency of virus infections or inability to recover from them, as determined from histories or from direct clinical observation. Janeway and associates (23) comment that although their group of children were highly susceptible to recurring bacterial infections, as is the general experience, they showed normal behavior toward the virus diseases of childhood and to vaccinia inoculation. Good & Varco (29) also emphasize this point. Chicken pox, poliomyelitis, mumps, and measles all occurred amongst their cases during the period of observation; in all instances the diseases ran normal courses and recovery was uneventful. Nor was there evidence of unusual occurrence of influenza, atypical pneumonia, or other virus infections in these patients. Yet these subjects were no more able to develop antibodies against a number of virus vaccines administered to them (including influenza, mumps, Western equine encephalomyelitis, and poliomyelitis) than to bacterial or other antigenic stimuli.

Several possible explanations for this apparent ability of agammaglobulinemic patients to acquire immunity (but not antibodies) to virus infections come to mind. The first is suggested by information gained from studies in man as well as animals that not all antibodies occur in the gamma portion of the globulins (13). Thus, Koprowski and co-workers (44) have found viral neutralizing bodies in different electrophoretic portions of the sera of vaccinated animals. But the evidence of Good & Varco (29) invalidates this nicety; their virus vaccine immunization trials indicated that neutralizing antibodies are not found in the serum as a whole against the number of representative viruses employed. Consequently, we must infer that demonstrable antibodies against viral agents are not formed in these patients, and that some other mechanism than circulating antibodies may be concerned in acquired immunity to some of these diseases. Whether, as Good & Varco suggest (29), there may be antibodies which are retained in tissues, or whether cellular alterations of the kind suggested above make the cells less congenial to parasitization by the virus, or whether some other process is at work, is not known, but it appears likely that a mechanism other than or in addition to conventional antibody resistance may be concerned here.

A point of related interest arises in respect to one of the bacterial infections—tuberculosis. To this reviewer's knowledge there has been no report of the occurrence of clinical tuberculosis in any agammaglobulinemic patient so far observed. (A possible exception exists in an instance personally communicated to the writer by Doctors H. H. Zinneman and W. H. Hall of the Veterans Hospital in Minneapolis. A 35-year-old male patient with agammaglobulinemia was found, on laparotomy several years before this diagnosis was made, to have enteric serosal granulomata and caseation and granuloma formation in a mesenteric lymph gland. No acid-fast organisms were demonstrable in these lesions, however. At the time of observation for

agammaglobulinemia no recognizable tuberculous process was evident.) This infection is general enough in its distribution that sufficient opportunities for exposure exist. Thus one would expect some instances of progressive disease amongst the agammaglobulinemic subjects so far encountered if they were unable to halt the progress of the bacillus through the acquisition of immunity. This disease differs from many other bacterial ones in being an intracellular infection during part of its course, and there is some evidence in this case that cellular (macrophagic) alterations rather than the acquisition of antibodies may be the responsible mechanism of acquired immunity in the experimental disease [Raffel (45); Lurie (46); Suter (47)]. The situation in agammaglobulinemic subjects appears so far to support this viewpoint.

A further point of immunologic interest with respect to agammaglobulinemia concerns the occurrence of atopic hypersensitive states, or of positive skin reactions to environmental and food allergens, in patients with this disease. Recent reports [Menzel *et al.* (48); Cann & Loveless (49); Campbell *et al.* (50); Rose *et al.* (51); Sehon *et al.* (52)] indicate that the antibodies elaborated by atopic individuals are to a considerable extent associated with the beta rather than the gamma globulin. Is this substantiated by the usual level of incidence of asthma, hay fever, and related syndromes in the group of agammaglobulinemic individuals so far studied? The reviewer has seen no reports upon this question. Isohemagglutinins also, though less strikingly than atopic reagins, differ somewhat in physicochemical properties from the majority of serum antibodies. The anti-A and -B substances have been described as migrating in the electrophoresis cell not as ordinary gamma globulin, but as an entity intermediate between gamma and beta globulins in mobility (53), and referred to as gamma 1 globulin. This is distinguished from the larger slow-moving component (gamma 2) in which most antibodies occur, and it appears to have the same properties as a protein produced by some patients with multiple myeloma (54). Despite its somewhat different character from the larger mass of gamma globulin, it is well documented now that agammaglobulinemic patients fail to manufacture these antibodies along with those belonging to the gamma 2 (31, 36, 37, 40), even after stimulation with appropriate heterologous erythrocytes (29, 40). As mentioned, however, these antibodies are not as segregated from "conventional" antibodies as are the atopic reagins.

X-RADIATION AND SUSCEPTIBILITY TO INFECTION

A topic relating to native as well as acquired resistance to infection is that concerned with the influence of radiation injury upon susceptibility to disease. Other agents, especially the corticoids and nitrogen mustard, are equally of interest from this standpoint, but current research seems to be focussed upon irradiation, and especially x-radiation. A number of recent reviews on this subject have appeared [Taliaferro & Taliaferro (55); Lorenz & Congdon (56); Zirkle (57); Talmage(58)], and another review in the present volume deals with this question also [Howland (59)].

An appropriate point of departure, for the purposes of this discussion, is the established fact that man and animals become much more susceptible to infections following total-body irradiation [Corper & Chovey (60); Taliaferro & Taliaferro (61); Clapper & Meade (62); Hammond (63)] with so-called median lethal doses, and that, in certain species, animals dying of irradiation overdosage almost always suffer spontaneous overwhelming systemic infections which appear to be the most frequent direct cause of death. This is true of mice [Miller & Hammond (64); Shechmeister & Adler (65); Hammond *et al.* (66); Boone (67)], and is preceded by a pancytopenia [Schechmeister *et al.* (68); Bond *et al.* (69)]. The type of radiation introduces some quantitative but no significant qualitative factor in these observations, as reported by Silverman *et al.* (70), using fast neutrons, and Vogel *et al.* (71), using the same rays and also gamma radiation. In other animals, including the dog, rabbit, and guinea pig, hemorrhage is said to take first place as a direct cause of irradiation mortality (56), although, in some studies, even in these species infection appeared in a majority of subjects [Bennett *et al.* (72)]. The human may fall into an intermediary place, as determined by the aftermath of atomic explosions [LeRoy (73); Tullis (74); Liebow *et al.*, (75)]. Direct studies of the influence of bacteria upon the fates of irradiated animals have been made in germ-free rats by the University of Notre Dame Lobund Institute group (76), and these have shown increased survival of germ-free over conventional animals following median lethal doses (400 r and 600 r), and lengthened survival at these and higher irradiation levels. Ultimate radiation injury per se was observed to be greater in the fatally affected germ-free animals presumably because lack of bacterial invasion permitted longer survival times.

The organisms commonly found in postirradiation septicemias are those we think of as pathogens *pro tem:* the Gram negative intestinal and related bacilli [Hammond (66, 77); Marston *et al.* (78)] which, mild enough under normal circumstances, can become more persistent and deadly than their more notorious brethren which we call pathogens, when normal physiologic conditions in the potential host become altered.

An important immunologic consideration which emerges here, as in aspects of innate immunity already discussed, is that of differentiation between altered susceptibility based upon a breakdown of native mechanisms of defense, and a failure of acquired immunity under the influence of irradiation. That acquired resistance as manifested by antibody production can be markedly impaired by x-radiation under certain circumstances is quite obvious [Talmage (58); Kohn (82); Paulissen & Shechmeister (83); Taliaferro & Taliaferro (84, 87, 88); Craddock & Lawrence (85); Dixon *et al.* (86); Maurer *et al.* (89); Hale & Stoner (90)]. This fact, however, does not necessarily account for the susceptibility of the irradiated subject to organisms in the intestinal tract unless normally existing insusceptibility is predicated upon acquired resistance derived from continuous immunization by enteric bacteria. There may be such a process at work, for Hammond and co-

workers (66) have found in normal mice that enteric bacteria penetrate the mucosa and appear in the mesenteric lymph nodes, where their progression is halted. Such systemic invasions could well account for continuous or intermittent spontaneous immunization.

The various possibilities, with respect to influence of irradiation upon increased susceptibility to infection, appear to be the following, singly or in combination:

(*a*) Nonspecific tissue damage permits ordinarily harmless bacteria to penetrate the tissues in large numbers.

(*b*) Native defense mechanisms of the host are interfered with, and permit the multiplication of organisms which would otherwise be sharply inhibited or killed.

(*c*) Pre-existent acquired immunity (antibodies) gained through repeated spontaneous exposures to enteric organisms is vitiated.

(*d*) The ability to acquire antibodies to organisms which have invaded the tissues is impaired.

Available evidence will be marshalled on each of these points.

The Effect of Nonspecific Tissue Damage

In the sequence of damage which follows median lethal irradiation, ulceration of the intestinal mucosa is an early finding, the damage being well on the way to repair by the fifth day postirradiation (68). Undoubtedly this permits massive invasion of deeper tissues by intestinal bacteria [Congdon *et al.* (79); Lawrence & Tennant (80)], and although Hammond and coworkers (66) have found that some intestinal bacteria penetrate the mucosa even of normal mice to appear in mesenteric lymph nodes, where their progression is halted, the difference between small and large numbers of organisms may in itself be a decisive factor, especially in view of other concomitant changes discussed below. Hammond and associates (77) do not consider the intestinal injury to be related to subsequent bacteremia because, as they point out, greatest susceptibility to *Pseudomonas aeruginosa* in irradiated animals occurs after the peak of intestinal damage has passed. This temporal relationship has been found by Kaplan *et al.*, also (81). It seems possible, however, that implantation of numerous bacteria may occur at the time of greatest local mucosal damage, and that proliferation of these bacteria to the point of bacteremia may not occur for several days thereafter, when other of the host's defenses have undergone injury, as noted below.

Interference with Native Defense Mechanisms

Cellular.—It is generally agreed from studies in the monkey [Schlumberger & Vazquez (91); Lushbaugh & Houck (92)], dog [Gleiser (93)], mouse [Spargo *et al.* (94); Shechmeister & Fishman (95)], and rabbit [Jacobson (96)] that major acute damage occurs to the lymphoid tissues within hours following median lethal irradiation, while severe injury to myelopoietic tissues comes later. Cells of the reticuloendothelial series, on the other hand, are relatively resistant (61, 68), and, in fact, continue to be phagocytic at a

time when lymphocytes, granulocytes, and erythrocytes have undergone marked destruction [Barrow *et al.* (97); Ingraham (98)].

The fact that granulocytes suffer severe injury should in itself account to a large extent for loss of native ability to resist potential parasites. In the mouse, survival following irradiation closely parallels the peripheral leucocyte level, as shown by Smith and co-workers (99, 100). Polymorphonuclear destruction in the mouse is at its height between the fourth and eighth days postirradiation, according to Shechmeister *et al.* (68).

In addition to quantitative considerations, polymorphonuclear cells appear to be qualitatively affected by irradiation, also. Shechmeister & Fishman (95) have found, with leucocytes of rabbits and rats, that ability to migrate is impaired by irradiation, and that in rats the maximum effect occurs between the third to fifth postirradiation days, concurrently with an observed increase in susceptibility to an induced infection with staphylococci. The same investigators (101) describe a decrease also in the phagocytic abilities of these granulocytes, as well as a diminution in bactericidal activity of leucocyte extracts against the same organism, again coincident with the period of greatest susceptibility to the induced infection. A secondary effect of the same kind was found at 10 to 13 days after irradiation. Wilkinson (102) observed deficient phagocytosis of *Pasteurella pestis* by rat leucocytes beginning a week after irradiation. Esplin and associates (103) failed to find this effect in the same animal species, but the timing of observations may have entered here, for with median lethal doses of x-rays the findings lean toward those of Shechmeister & Fishman, as described by Rosselet & Sarian (104) in man, and by Blair (105) in dogs.

The macrophage system in contrast to the microphages appears to be resistant to irradiation. This is relative, for Chrom (106) found that irradiated mice cleared intravenously injected *Salmonella* more slowly than did normals; and Kaplan and associates (81) concluded that one defense mechanism impaired in irradiated mice injected intramuscularly with streptococci is the filtering function of the regional lymph gland. Once organisms reached the blood stream, the progress of events was no more rapid in irradiated than in nonirradiated animals. Barrow and associates (97), however, found no effect of large doses of irradiation on clearance of intravenously injected colloidal radiogold from rabbits, nor did Ingraham (98) or Brecher *et al.* (107) find decreased deposition, in irradiated rabbit liver or spleen, of radioactively tagged erythrocyte stromata. Many reports indicate that extensive erythrophagocytosis by reticulum cells occurs in severely irradiated subjects.

Kaplan *et al.* (81) question whether the ability of reticuloendothelial cells to clear the blood of inert substances is a proper measure of their capacity to take up and dispose of virulent bacteria, and, as a matter of fact, Donaldson *et al.* (108) and Esplin *et al.* (103) have found that irradiation inhibits the disintegration of erythrocytes and bacteria within macrophages. On the other hand, tests with virulent bacteria may not properly reflect the ability of these cells to deal with the spontaneously infecting enteric organ-

isms which cause most of the difficulties in irradiated animals. Perhaps a valid conclusion may be that cells of the reticuloendothelial system are to some extent impaired functionally, but relatively only to a small degree.

The obverse of these studies correlating cell damage with occurrence of infections is afforded by experiments dealing with the effects of protection against irradiation damage upon the incidence of infection. The most effective of the protective measures yet devised consists of shielding even a small portion of hematopoietic tissue, such as a femur, or of potentially hematopoietic tissue, such as the spleen in mice (56). Alternatively, minced tissues of these kinds can be injected into irradiated subjects. For protective purposes, hematopoietic tissue appears to be essential [with possible exceptions as suggested by Lorenz & Congdon's (56) success with reticulum cell sarcoma], as shown by the ingenious experiments of Storer *et al.* (109) using the tail of the mouse. The tail ordinarily contains fatty marrow, but if it is implanted for a time in the abdominal cavity it develops red marrow (110). Shielding the former is not protective, shielding the latter is. Synchronously with protection against irradiation, susceptibility to bacterial infection diminishes [Lorenz *et al.* (111, 112); Jacobson *et al.* (113); Silverman & Cole (114)]. What the general nature of the protective activity of hematopoietic tissue is, has not yet been determined. It may provide a humoral stimulus to recovery of the same elements of the irradiated subject (56); [Jacobson (115)] it may seed fresh elements to initiate regeneration or, as Storer *et al.* (109) suggest, the small amounts of unirradiated tissue may themselves serve as a focus for sufficient hematopoiesis to support life until spontaneous regeneration occurs. Specifically, these authors believe that the essential substitute provided by protected tissue may consist of undamaged blood leucocytes. There may be a combination of the events suggested, of course, but the potential importance of an adequate blood level of granulocytes for antibacterial protection during the period of most extensive radiation damage seems apparent. However, Jacobson's (116) finding that removal of the shielded spleen only 5 minutes after irradiation does not obviate protection makes the granulocyte replacement hypothesis unlikely, though still tenable (109). Furthermore, Lorenz & Congdon (56) have been able to protect with reticulum cell sarcoma, and Jacobson (116) by shielding of the appendix; both tissues are essentially devoid of granulocytes.

Whichever of these hypotheses of protection may eventually prove to be correct, the important point with respect to mechanisms of native resistance is that hematopoietic, and specifically granulopoietic, recovery is considerably hastened by the measures described, and simultaneously there is decreased susceptibility to infection. The two effects may be coincidental rather than causally related, but the role of the blood phagocytes in resistance is too firmly established to make this probable. As is well known, in agranulocytosis due to various causes the subject becomes highly susceptible to infection.

Alterations in humoral batericidal activities.—Generalizations, however, are not dependable in the realm of host-parasite relationships. In the case

of at least one of the organisms which is a frequent cause of infection in irradiated mice, *Esch. coli*, Rowley (117) has shown that phagocytosis by granulocytes is not, under normal circumstances, a decisive factor in protection. Strains of *Esch. coli* which are virulent for the normal mouse are as well ingested as are avirulent strains, but while the first kills the animal, the second disappears from it. In this case a humoral factor, properdin, is more importantly involved in suppressing avirulent *Esch. coli*, and if this is removed the animal becomes susceptible to the avirulent bacillus (19). Among the species of animals tested by Pillemer *et al.* (16), the mouse contains a relatively high level of properdin, the blood level of which can be manipulated by injections of zymosan, the yeast derivative which combines with properdin, as well as by bacterial cell wall components (see above).

It is surprising that a plasma factor is revealed as an important element of native immunity in the mouse, since Marcus *et al.* (118) recently reported the inability of normal mouse serum to affect adversely any of a number of bacteria, including enteric organisms, *in vitro*. But this appears to be a paradoxical situation which exemplifies the dangers of making deductions from any one line of evidence. Rowley (117) also failed in his studies with *Esch. coli* to find any bactericidal influence of normal mouse blood or serum *in vitro*, yet found it in high measure *in vivo*. *In vitro* it could be detected only if the complement of another species—guinea pig or man—were added. Mouse complement is well known to be deficient in one component, C'2, and since complement is necessary for properdin activity, this lack presumably accounts for the failure of the *in vitro* tests. But how does one account for bactericidal activity *in vivo?* This must depend upon some difference of activity of complement in the body from that shown by freshly drawn blood of this species outside, or upon some other as yet unexplained difference in a property of blood having to do with the properdin system and manifesting itself only *in vivo*.

If properdin, in this instance at least, has to do with the defense of the normal host against one of the bacteria which overwhelms it after irradiation, is there any evidence that irradiation adversely influences this property? Pillemer *et al.* (116), with sera collected from rats at various intervals after total body irradiation, found that by the second day the level of properdin had fallen to one-fifth or less of normal, and by seven days it had virtually disappeared. Complement, on the other hand, increased in concentration during this period. It is stated that these sera lost their normal bactericidal and virus-neutralizing properties, though particulars are not supplied. Work of Stroud & Brues (119) is cited to the effect that irradiated mice may be partially protected by injections of Cohn's serum Fraction III, and it is in this fraction that most properdin occurs. Further, Pillemer's group observed partial protection of irradiated rats by the intravenous injection of purified bovine properdin on the second, fourth, and seventh days after irradiation. More recently, Pillemer's group (120) again described protection of irradiated mice and rats by injections of purified properdin, of bovine and human

origins. Furthermore, it was found that protection against irradiation could be manipulated by injections of zymosan, the properdin-combining substance.

It would be of interest to know whether spleen shielding or other maneuvers which protect against irradiation damage also keeps intact the properdin content of the plasma, or allows a rapid return of this substance to a normal level.

Marcus & Donaldson (121) have also made observations implicating failure of nonantibody humoral mechanisms of immunity in irradiated rabbits. The bactericidal activity of the serum was depressed between the fifth and fifteenth postirradiation days. In a later study (122) designed to establish the specific mechanisms affected, it was found that irradiation did not give rise to an inhibitor of bactericidal activity, that complement was not damaged, and that "normal" agglutinins against the organism studied—*Bacillus subtilis*—remained unimpaired. Despite these facts, the serum of irradiated subjects failed to kill *B. subtilis* as did normal rabbit serum.

Fishman & Shechmeister (101) made different observations in studies of rat serum and the staphylococcus. Serum from irradiated animals did not lose its inhibitory properties, even on the third day when susceptibility to induced infection with the coccus became most marked; in fact, the bactericidal activity at this time appeared to increase over the normal. This is not surprising; in host-parasite relationships we cannot fasten upon one sequence of events as establishing the pattern for all cases. It seems quite reasonable that properdin may not influence the staphylococcus, and that in this instance, as indeed other previously quoted work of Shechmeister's indicates, granulocytes are more important to native defense than are humoral antibacterial factors.

As to alterations in normal tissue and blood constituents by irradiation, other than those already discussed, knowledge is as yet fragmentary. Changes in adrenal function may prove of interest. According to Schlumberger & Vazquez (91), a marked increase in weight of the adrenals occurs in rats dying within a few days after irradiation, and in monkeys some increase in the size of these organs is noted one to three weeks postirradiation. This might suggest an effort on the part of these glands to compensate for depletion of their products, and indeed, a urinary loss of cortical steroids follows lethal total body irradiation in pigs [Brayer and associates (123)] especially in the first 24 hours following irradiation [Ellinger (124)]. Administration of cortisone, however, does not alleviate the consequences of irradiation damage; Ellinger (124) and Smith *et al.* (125) found this and ACTH to hasten death. That other cortical factors may be protective, however, is suggested by the ameliorative effect of DCA or whole adrenal extract administered to adrenalectomized irradiated rats.

Amongst other changes observed in irradiated animals, which cannot yet even be speculated upon with respect to susceptibility to infection, are alterations in serum components including a decrease in albumin and some of the faster moving globulins and beta lipoproteins, and increases as well

as decreases in various glycoproteins [Goldwater & Entenman (126)]. According to Edelmann (127), the serum of irradiated rats causes death in unirradiated adrenalectomized rats or mice, inducing hematologic effects similar to those which follow irradiation. The significance, if any, of such events for the question under discussion remains to be clarified; they are mentioned chiefly to point out that the more obvious mechanisms discussed may not necessarily account in all respects for the infectious sequelae to irradiation.

Effect of irradiation upon pre-existent acquired immunity.—In the ordinary course of events the normal subject may acquire antibodies to enteric bacteria as well as a variety of other environmental infectious agents, through continuous or intermittent spontaneous vaccination. So-called "normal" antibodies against bacteria and various erythrocytes occur in man and animals in patterns consistent with the species studied [Landsteiner (128); Raffel (13)]; whether some of these are "normal" in the sense of being intrinsic to the species, as could be the case if some globulin molecules were so synthesized purely by chance as to react with these substances, or whether they all represent spontaneously acquired responses to the antigens of environmental agents and substances, is a moot point. For purposes of their potentially protective properties, however, this may not be important; since such antibodies exist they may provide protection, and irradiation may interfere with this. If such spontaneously acquired antibody immunities do account for normal insusceptibility to infection by enteric bacteria, it is easy to postulate that even though this were at a lower than effective level at the time of irradiation, it could perhaps be rapidly bolstered by the secondary immunogenic stimulus provided by the bacteria which invade deeper tissues in the wake of the early intestinal ulceration (79).

As for injury of preformed potentially protective antibodies by irradiation, the evidence available adequately indicates that this could not be a factor of importance in determining postirradiation bacteremia. A number of careful studies have shown that while x-irradiation can seriously interfere with the formation of antibodies if applied in advance of the antigenic stimulus, it does not diminish responses if applied after, and furthermore that antibodies already existent are not altered in quantity or combining activity (58) [Kohn (82); Paulissen & Shechmeister (83); Taliaferro & Taliaferro (84, 87, 88); Craddock & Lawrence (85); Dixon *et al.* (86); Maurer *et al.* (89); Hale & Stoner (90)].

The second portion of the proposition postulated above, that antibodies acquired to enteric bacteria through primary spontaneously occurring stimuli may, after irradiation and more overwhelming exposure to these organisms, develop anamnestically to higher levels, is still an unsettled point. Dixon *et al.* (86) and Silverman & Chin (129), using protein antigens, found no interference by irradiation with the ability of the rabbit to respond to the secondary antigenic stimulus, whereas Taliaferro and co-workers (87, 130) with erythrocytes as antigen in the same species, found the anamnestic response to be suppressed as well as the primary response. It would appear that the form in which antigens are presented to the tissues may account

for this difference; elucidation of this point alone may uncover some of the mystery of antibody origin. In which of these ways the animal body may respond to bacteria anamnestically is yet unknown.

A fair generalization may be that the influence of irradiation upon susceptibility to infection does not depend upon interference with antibodies which may already have been acquired to the eventual infectious agent, but that it can interfere if the bactericidal activity of antibody requires a radiosensitive accessory such as the leucocyte. Some direct tests of this point have been carried out. Paulissen & Shechmeister (83) found that although mice vaccinated with *Salmonella enteritidis* prior to irradiation and then challenged with living organisms required a larger infective dose to kill them than did nonimmunized irradiated animals, they were still more susceptible to the agent than untreated controls. Hale & Stoner (90) observed essentially the same kind of results with influenza A virus in immunized mice, as had Amoss *et al.* (131) earlier with poliomyelitis in monkeys. Smith *et al.* (132) report results which are more difficult to interpret. Mice were deliberately vaccinated with the variety of bacteria known to be the most frequent causes of septicemia in irradiated animals. These included *Ps. aeruginosa*, *Esch. coli*, a paracolon bacillus, and an alpha hemolytic streptococcus. When these animals were then subjected to sublethal irradiation and deliberately challenged with these bacteria, they were protected, indicating that irradiation had not damaged previously acquired antibodies. If, however, such vaccinated animals were subjected to lethal irradiation, they fared no better with respect to spontaneously occurring infections than did nonvaccinated mice. In view of this report, and a similar one by Fulton & Mitchell (133), it is interesting to consider how irradiated animals might handle spontaneous infections if they were given passive antibodies against the usual infecting strains. This might clarify whether the observed interference with acquired immunity lies in a defect in the functioning of antibodies (against which evidence has been cited), or whether damage to elements accessory to the efficient functioning of antibodies, e.g., the leucocytes, explains the end result. The findings of Hale & Stoner (134) in irradiated mice receiving pneumococcus and antiserum may support the latter explanation, for the serum did not prevent mortality. Surprisingly enough, however, transfusions of blood or leucocytes did not help these animals with acquired antibodies. The combination of passively administered antibodies and transfused leucocytes would be expected to prove protective; this point should be pursued further.

Effect upon ability to acquire antibodies.—As discussed before, available evidence conclusively demonstrates that x-irradiation applied in sufficient dosage and at the proper time—within a rew days to a few hours before an antigenic stimulus—will interfere almost entirely with the subsequent production of antibodies. In the present connection, the point at issue is whether such a failure to acquire antibodies may in any degree explain the increased susceptibility of the irradiated animal to infection. From the standpoint

of temporal appearance of infection, this could be a factor, since as Chrom (106), Miller *et al.* (135), Shechmeister and co-workers (95, 101), Kaplan *et al.* (81), and a series of predecessors (61) have found, most spontaneous bacteremias in mice occur in the second week after irradiation. A failure of the acquired ability to deal with the bacteria could result in septicemia at about this time.

Smith & Gump (77) compared the extent and rapidity of the antibody-producing capacities of rabbits and rats to their subsequent abilities to withstand median lethal doses of irradiation. Animals were first tested for their responses to two commonly employed antigens, egg albumin and sheep erythrocytes, and were subsequently irradiated. No correlation was found between the relative ability to respond and subsequent survival. This might have been expected, since sufficient dosages of irradiation in any case obliterate the capacity to form antibodies, whatever the ability of the normal subject in this regard.

More direct information on the point could perhaps be gained from the passive transfer of appropriate antibodies to irradiated animals during the period, beginning perhaps four or five days after irradiation, when in the normal course of events they would be expected to have formed their own antibodies. If the administered immune bodies should prove helpful, then it could be fairly inferred that the failure of the irradiated animal to produce them actively is a factor leading to its increased susceptibility to infection. The failure of Hale & Stoner (134) to protect irradiated mice against the pneumococcus with passively administered antiserum suggests that susceptibility depends upon a more extensive dysfunction than antibody manufacture. As stated earlier, however, these investigators had no more success even when leucocytes were added to the transfer. Other work also suggests that failure to acquire antibodies may not explain irradiation septicemia. Thus, Kohn (82) has shown that the ability to manufacture antibodies begins to recover on the seventh day after irradiation in rats, and this is the case also in rabbits (88, 130). If this is generally true, irradiated animals might be expected to have formed responses in time to prevent bacteremia.

In general summary, the evidence is strong that cellular (granulocytic) and humoral (properdin, and other) factors of native defense may be sufficiently altered by x-irradiation to account for increased susceptibility to septicemic infection by enteric and other organisms. It seems probable that the first step in this direction results mechanically from damage to the intestinal mucosa, which permits ordinarily harmless bacteria to penetrate tissue boundaries in large numbers. Whether impairment of acquired specific immunity—antibody production—also plays a part in this process is less clear. Since preformed antibody is not injured by irradiation, it seems dubious that any resistance acquired through spontaneous immunization of the host prior to irradiation should be interfered with. It is possible that interference with the *de novo* antibody response to bacteria which have invaded beyond the tissues injured by irradiation may be a factor in hindering the

ability of the host to terminate the infection once under way, but the scanty evidence available does not favor this viewpoint. Further investigations employing the transfer of preformed antibodies to irradiated animals might be helpful in clarifying this question.

The evidence forming the basis for this summary is fragmentary, relating a limited number of hosts to a limited variety of bacterial species. A more complete formulation would require specific investigations to determine the nature of the mechanisms of defense of various animal species to the different bacteria which may spontaneously infect them following median lethal irradiation, followed by studies to learn which of these mechanisms are impaired by irradiation. As an example, the work of Rowley (117) with *Esch. coli* infection in the mouse has shown quite clearly that the normal animal depends largely upon the properdin content of its plasma for protection, and that irradiation (19) decreases the level of this substance. The same host may rely upon other mechanisms, including spontaneously acquired antibodies, for its defense against other potential parasites. The same considerations apply to other species of experimental animals as well as to man.

It should be noted in closing this review that studies of irradiation in respect to infection and immunity have so far been channeled into rather restricted avenues. Most work has concerned itself with three broad questions: the influence of irradiation upon susceptibility to infection, upon the ability to acquire antibodies, and upon already existing acquired immunities. No studies appear to have been made of the possible influence of irradiation upon the acquisition of resistance, as distinct from antibodies alone. There exist a number of instances of infectious diseases, including anthrax, tuberculosis, and certain virus infections, in which there is some question about the importance of antibodies to acquired immunity. It would be of considerable interest to determine if irradiated subjects may acquire immunity to these infections despite the suppression of the antibody response.

IMMUNOLOGIC PARALYSIS

Under certain circumstances not related to extraneous influences such as irradiation and other factors previously discussed, the body may fail to recognize a foreign antigenic substance as a stimulus for the immune response. This fact, termed "immunologic paralysis," has been known for a number of years in one limited instance discovered by Felton (136) to follow the injection of an excess of pneumococcal capsular polysaccharide (SSS) into the mouse. Interest in this surprising phenomenon has been stimulated recently by the experimental findings that adult, newborn or fetal tissues exposed to other antigenic materials may, under certain circumstances, similarly refuse to react to it immunologically. These observations, aside from their intrinsic interest, may have a number of practical implications with respect to the treatment or prevention of hypersensitive states, the prevention of transfusion reactions and neonatal disease, the problem of tissue grafting, and the timing of vaccination of infants.

The nature of the evidence existing in this field is not always readily in-

terpreted; consequently, for the sake of clarity, it will be discussed under several headings: first, "immunologic paralysis" in adult subjects, next an apparently similar phenomenon in newborn animals, and finally, related occurrences in the fetus.

Immunologic Paralysis in the Adult

Felton's first inkling of the existence of "immunologic paralysis" came in 1940 from the results of human immunization with pneumococcal SSS (137). One to 5 per cent of subjects failed to produce antibodies to these ordinarily effective antigens. Later (136) it was found that 0.5 mgm. quantities of the polysaccharide regularly failed to stimulate antibody formation and acquired immunity to the pneumococcus in mice, although smaller quantities did both very readily. Earlier work pointing in the same direction is reviewed by Felton *et al.* (138), and confirmation has come from Stark (139) and Morgan *et al.* (140), who believe that the well-known failures to immunize rabbits with pneumococcal SSS in the past, generally attributed to species differences of unknown kind, may have been caused by the use of excessive vaccinating doses, since very small doses are successful.

The paralysis induced by one dose of polysaccharide in mice persists virtually for the lifetime of the animal (138), and it is more or less specific for the antigen used [Morgan *et al.* (141)]. Felton *et al.* (138) found that following administration of Type I polysaccharide there was some inhibition of later antibody formation against Type II substance, but in experiments in which Types I, II, and III polysaccharides were employed as paralyzing agents and complete cross tests were subsequently carried out, these investigators found only this one instance of failure of specificity. Hanan & Oyama (142) noted similar intimations of nonspecificity of inhibition of antibody formation in young rabbits given protein antigens; these exceptions may weigh considerably in the final interpretation of the mechanism of this paralysis.

Other antigens have been tested in large amounts in other species of animals. Dixon & Maurer (143) repeatedly injected very large amounts of serum protein into adult rabbits and found that prolonged suppression of antibody formation was not attainable, but some effect occurred, and this was specific. Johnson *et al.* (144) injected doses of about 1 gm. each of bovine globulin into rabbits for five days and found no antibody responses in some of the animals—those which retained antigen for between 40 and 50 days. Paralysis lasted for six months or longer in some animals.

An apparently related phenomenon has been reported by Battisto & Chase (145, 146) in respect to the development of both contact and anaphylactic sensitivity by guinea pigs to allergenic chemicals. In this case, prefeeding the chemicals rendered the animals relatively unamenable to subsequent sensitization of either type.

Several interpretations have been offered of the way in which paralysis of the immunologic mechanism may be effected. It seems to be most often held that the mere fact of persistence of antigen in the body in some way

interferes with antibody production [Johnson *et al.* (144)], or that persisting antigen may neutralize antibodies as they are formed.

As for the first viewpoint, certain facts support it. Felton *et al.* (147) found pneumococcal polysaccharide still present in the livers of mice 15 months after the paralyzing injections. In later work, however (148), even the smaller immunizing amounts of this substance were found to be recognizably persistent in the tissues after several weeks, long after antibody had appeared in the serum. Strangely enough, of the series of tissues tested in the various paralysis experiments reported here, heart proved to yield the most pneumococcal antigen, while in the immunized series, skin was the highest in content of injected substance. Johnson *et al.* (144) observed in their experiments with protein antigen in rabbits that the animals which failed to eliminate large doses of injected material rapidly were those which for the most part failed to produce antibodies. One might argue conversely that animals which fail to produce antibodies fail to eliminate antigen rapidly, for Talmage and co-workers (149) amongst others have shown an accelerated curve of antigen disappearance from the blood with the appearance of antibody. These latter authors believe, however, that the presence of antigen in the tissues, or perhaps in the antibody-producing cells, may in some way inhibit antibody manufacture.

It is difficult to agree with this viewpoint as a generalization if one considers the evidence cited above in which polysaccharide was found to persist even in responding mice. Indeed, Heidelberger (150) believes that the persistence of pneumococcal polysaccharide and of a polysaccharide of *Salmonella typhosa* in the tissues may account for the prolonged plateau of antibody response occasioned by them, and McMaster *et al.* (151) have found even protein antigens to persist in mice for up to 14 weeks, and in rabbits for eight weeks, beyond the time of disappearance of antibody responses to them. Haurowitz & Crampton (152) employed a radioactively marked protein antigen in rabbits, and found it in liver cells 29 days later in amounts small in absolute weight but large in terms of molecular numbers. Erickson *et al.* (153) used tobacco mosaic virus as an antigen identifiable by several means in the tissues, and observed it by electron microscopic examination after 15 days, though the antibody response to it had already begun to decline at this time. Detailed discussions of these points are provided in recent reviews by Coons (154) and Haurowitz (155) and in a report by Dixon (156). Moreover, the well-known fact of elaboration of antibodies during the course of infectious diseases, while the causative agents are still active in the tissues, should preclude so simplified an explanation. Such agents may persist for long periods even after recovery from infection; Smadel *et al.* (157) and Parker *et al.* (158) have recovered from patients the rickettsiae of scrub typhus and of Rocky Mountain spotted fever, respectively, as long as 12 months after recovery from these diseases, and similar persistence of rickettsiae has been recognized in the case of epidemic typhus fever, where recurrences (Brill's disease) may appear years after the initial infection.

If one entertains the viewpoint that antigen in the tissues may interfere with appearance of serum antibodies not simply because of its presence, but because of its quantity, then one may invoke the second suggestion already mentioned that immunologic paralysis consists not of failure of antibody production, but rather of continuous neutralization of antibody as it is formed so that it never becomes detectable in the blood stream. There is evidence that antigen-antibody complexes may occur in the blood. Sternberger *et al.* (159) found such complexes, dissociable by treatment with alkali at low temperature, in the blood of rabbits following one large intravenous injection of beef albumin. Singer & Campbell (160, 161) have also provided evidence on this point, as have Gerstl *et al.* (162).

Prolonged paralysis on the basis of antibody neutralization might require that the antigen combine with a considerable quantity of of antibody. Dixon *et al.* (163) tested this point by paralyzing mice with Type III SSS, then injecting I^{131}-labelled rabbit antibody against this antigen and following its disappearance from the circulation. Antibody was taken up and apparently destroyed and excreted, for no I^{131} could be found in the tissues; the antigen meanwhile apparently persisted, repeatedly combining with antibody until no more was available.

In the immunologic paralysis described by Battisto & Chase (145) as occurring in guinea pigs fed allergenic chemicals prior to attempted sensitization, measurements were also made of rates of clearance of injected quantities of appropriate antibody, to determine if this might be neutralized by depots of antigen established by the feeding. In this case, no such effect was observed.

Compounding the difficulties of interpretation is the report by Felton *et al.* (138) that, in face of the efficacy of isolated SSS of the Type I pneumococcus in inducing paralysis in mice, and that of acetone-killed whole bacteria to do the same, several other vaccines of the same organism prepared in different ways (e.g., by heat or formolization) fail to induce paralysis in any dose. Furthermore, when mice had been paralyzed with a preparation of SSS, they could subsequently be made to respond to such vaccines of homologous antigenic type.

It appears from these varied experiences that no satisfactory explanation for immunologic paralysis caused by excessive doses of antigen in adult animals is yet at hand. The evidence is not clear that antigen persisting in the tissues discourages antibody formation per se or neutralizes antibody as it is formed, or even necessarily interferes with subsequent immunization by the same antigen presented in a different form.

Tumor transplantation.—Closely related to the question of immunologic paralysis are studies made in recent years with transplantable tumors in mice. In the transplantation of normal tissues it is well known that homografts, i.e., transplants from one to another member of a species, will not take. An exception to this rule is found in the case of single ovum twins; and, what is practically the same genetically, in highly inbred animal

strains in which brother-sister matings have been successively carried out to the point where practically complete genetic homogeneity exists amongst members of the strain [Snell, 164)].

There is a growing body of evidence which suggests that the failure of grafting of normal tissues between individuals has an immunologic basis [Good & Varco (29); Medawar (165); Amos *et al.* (166); Adler (167); Gorer (168)], and the same considerations appear to apply in the case of transplantation of noninfectious tumors (164); [Hoecker (169)] with a few exceptions. Some years ago, Casey (170), and later Snell and co-workers (171), found that the injection into a normally resistant mouse of a moderate quantity of lyophilized tumor tissue would lead to susceptibility to the tumor a short time later, and that this state might persist for as long as 45 weeks [Kaliss & Day (172)]. Some normal tissues of the donor mouse, especially spleen and kidney, have the same ability to induce acceptance of tumor. Smaller doses of tumor tissue, on the other hand, may increase resistance to the transplant (where resistance is not already normally complete) [Kaliss (173)]. In practically all respects, this evidence appears to parallel that found with antigens in adult animals described above. An outstanding point of difference, and one which, so far as the reviewer is concerned, defies interpretation on any basis which might account for immunologic paralysis, is the fact that not only tumor tissue, but the serum obtained from a heterologous animal (e.g., rabbit injected with the tumor) will, if administered to a recipient animal, make it susceptible to tumor transplantation [Kaliss (174)].

Kaliss (175) has attempted with these same techniques to influence the survival of normal tissue homografts in mice. These efforts were unsuccessful with skin grafts, and equivocal with spleen.

Immunologic Paralysis in Young Animals

Young rabbits appear to be more susceptible to immunologic paralysis than adults following even moderate doses of protein antigen. A group of newborn animals to which Hanan & Oyama (142) administered small doses (0.10 to 1.0 mgm.) of alum-precipitated bovine serum albumin three times a week for three and a half months, failed to produce antibody detectable by serologic tests, Arthus reactivity, or ability to transfer anaphylactic sensitivity to guinea pigs. These same doses were shown to be effectively immunogenic in animals which had attained two and one-half months of age. Again here, as in some of the experiments with adults mentioned above, there was some indication of nonspecificity of the unresponsiveness, for a proportion of the animals receiving bovine albumin since birth and given egg albumin in addition after two and one-half months, failed to respond to this antigen also.

An interesting sidelight in this study was the determination of the development of plasma globulin from the time of birth. It is well known that gamma globulin is at low level at birth; in rabbits it appears to be absent. This was found to appear at about six weeks, and in the immunologically

paralyzed animals it developed at the same rate and in comparable quantities as in controls.

A second report dealing with the unresponsiveness of newborn animals is that of Dixon & Maurer (143). Again, prolonged unresponsiveness was found to follow administration of protein antigen to rabbits beginning at the time of birth. This failure to respond persisted until the termination of the experiments, up to ten months.

The mechanism of this type of unresponsiveness is not known, but in view of the small doses of antigen with which it can be accomplished, those authors [Dixon & Maurer (143)] who believe that adult paralysis may depend upon neutralization of antibody as it forms by residual antigen in the tissues, incline to the viewpoint that the phenomenon observed in the young may be related rather to an acceptance of foreign substances by newborn animals as "self components"—a concept to be described in the following section.

Immunologic Paralysis During Fetal Life

Most stimulating perhaps, from the standpoints of practical implications as well as the philosophy of immunology, is the final instance of immunologic paralysis; this has been observed to occur in postnatal life after exposure of the fetus to a foreign antigenic substance *in utero*.

This story properly begins with observations made in the past of the occurrence of two types of erythrocytes in dizygotic cattle twins. This results from the fusion of vascular channels during fetal development with intermingling of embryonic cells, and the establishment of hematopoietic elements of each of the twins in the other [Owen (176)]. This situation is termed "erythrocyte mosaicism"; it occurs in sheep also [Stormont *et al.* (177)], and recently a most interesting report from England described its appearance in a 25-year-old woman, a twin whose brother died at an early age, and whose cells are of types O (61 per cent) and A.

In dizygotic twin cattle, skin homografts frequently survive [Anderson *et al.* (178)]. Presumbably this acceptance, not seen amongst ordinary siblings, is a consequence of the same kind of intimate exchange between fetal cells which serves to established islands of hematopoiesis; in this instance, however, the consequence reveals itself more simply as a failure of each twin to regard tissue elements of the other as foreign in the immunologic sense. Analogously, the woman with O and A blood cells possesses antibodies against B cells, but not against the A which were presumably implanted through a common vascular channel from her brother. It appears, in short, that during prenatal life the body is not only incapable of responding to foreign antigenic substances, but that this incapacity once established may persist indefinitely postnatally.

With these facts as a basis, Billingham *et al.* (179) injected into mouse embryos on the fifteenth or sixteenth day of gestation a small quantity of mixed adult tissues (testis, kidney, and spleen). Four days later the young were born; after eight weeks these were grafted with skin from the heterol-

ogous mouse strain which had supplied the tissue inoculum. In five instances described, three grafts took successfully. One of the recipients was again grafted seven weeks later, and again accepted the heterologous skin without reaction. Tolerance was not necessarily lifelong; in one instance, at least, the perfectly incorporated graft underwent necrosis after 91 days. The tolerance was entirely specific; skins from other donor strains were rejected at the same time that the acceptable graft underwent no change whatever [Billingham *et al.* (180)]. Similar findings have been made with chickens and rabbits (180).

Strangely enough, in contrast to the findings of unresponsiveness occasioned by tumor tissues in adult mice, and by small doses of antigens in newborn rabbits, these investigators have found very little evidence that newborn mice inoculated with tissues become immunologically unresponsive to subsequent grafts as do fetuses. The limits of time of effective inoculation for this purpose are fairly precise; fetuses up to the thirteenth or fourteenth day are killed by the procedure, and on the other hand, inoculation within 12 hours of birth results in subsequent tolerance to grafts in only 5 to 10 per cent of instances (180). This last fact is true of chickens as well [Cannon & Longmire (181)].

The possible mechanism underlying this form of "immunologic paralysis" is discussed by Billingham *et al.* (179) in terms of the hypothesis of "self marker" units proposed earlier by Burnet & Fenner (182). In essence, this supposes that those molecular configurations which are present during embryonic life are "recognized" as being part of the self by the developing fetus, and that this recognition persists into postnatal life so that such substances are not responded to as foreign antigenic materials.

Whether the various instances of immunologic paralysis so far described represent features of a common phenomenon cannot yet be ascertained. It may be possible that relatively large quantities of antigen in the adult may depress the same aspect of responsiveness as is affected by small quantities in the newborn, and perhaps even smaller stimuli in the fetus. Certain irregularities must be clarified before a common basis can be sought, including, for example, the susceptibility of adult mice to influence by relatively small amounts of neoplastic, but not of normal tissue, and the strange ability of an antiserum against neoplasm to induce a similar state of nonreactivity to tumor transplant as does the tumor tissue itself.

The presently most favorably regarded mechanism of "immunologic paralysis" in the adult animal given large quanties of antigen is that which supposes excessive antigen to neutralize antibody as it is produced. Some evidence against this viewpoint has been quoted from the work of Battisto & Chase (145), and Dixon & Maurer (143), using protein antigen in newborn rabbits, found that immunologic unresponsiveness persisted long after any antigen could be demonstrated in the tissues; in this case there could be no neutralization of antibody. Additional evidence against this viewpoint is contained in the observations of Billingham *et al.* (180) that mice made unresponsive to skin grafts by the appropriate treatment described could then

be converted to the responsive state if they were given fragments of normal lymph node from a mouse of the same strain. In this event the transferred cells participated in the immunologic response [Chase *et al.* (183); Harris *et al.* (184, 185)], and this response was not neutralized by persisting tissue antigens which had been administered prenatally.

Implications of Immunologic Paralysis

A variety of possible consequences of this immunologic information comes to mind. One is the use of large "paralyzing" quantities of antigen to forestall the possibility of antibody formation at an inopportune time, as in the preparation of an Rh negative mother for a future pregnancy in which the child may be Rh positive. It has been suggested by Mitchison (186) that nature may provide protection to unborn generations of Rh positive individuals through the following process: during the course of fetal development of an Rh negative female in an Rh positive mother, there may be accidentally implanted in the fetus maternal cells bearing the Rh antigen. In postnatal life this individual would presumably fail to recognize this antigen as an immunologic stimulus, and incompatible children born to such an individual would consequently not suffer the neonatal disease. This may be a factor accounting for the observed occurrence of erythroblastosis fetalis in only a minor proportion of infants in whom it might, on the grounds of antigenic incompatibility, be expected. Billingham and coworkers (180) in the same vein postulate that the accidental incorporation of maternal cells in the fetus may make it less resistant in later life to tissue transplants from the mother.

The possibilities of prophylaxis for hypersensitive states by prefeeding allergenic substances in the case of contact sensitivities as suggested by Chase, or by the administration of relatively large systemic doses of environmental allergens to potentially allergic children (i.e., children with suggestive family backgrounds) may be worth consideration.

Finally, the experimental findings described may be of especial interest in relation to vaccination of human infants. It may be wise to review the pediatric procedures currently in use with respect to time of administration of vaccines to infants. Undoubtedly, however, species differences exist in chronologic ability to respond to antigens with respect to development at birth, for it is stated that, unlike the case in lower animals, newborn infants can produce antibodies to tetanus and diphtheria toxins [Osborn (187)], though at a more sluggish rate than after the passage of some weeks.

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PEDIATRICS

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Following the pattern of previous reviews, this one was not intended to be comprehensive, but rather selective; contributions to knowledge affecting the health of children are too numerous for completely adequate exploitation in these few pages. Notes made at several current medical meetings have permitted brief mention of some items that have not yet been published at this writing.[1] Following a pattern set by previous authors, this writer has happily received helpful suggestions from many members of his staff.[2]

In the pattern of producing this volume, there must necessarily appear some repetitions; opposing, or at least controversial, comments concerning critical reviews dealing with work of concern to several specialities, and interpretations varying with current interests of the several authors. Undoubtedly much important work will be missed, but a sincere effort has been made to select for review those contributions we believe have been most significant in the framework of pediatric teaching and practice.

Neurologic Disorders

Lennox (1) has further documented the thesis, already quite generally accepted, that "febrile convulsions" in young children probably represent a mild form of truly genetic epilepsy, and that the prognosis in both febrile and non-febrile genetic epilepsy is reasonably good—"less than 5 per cent of patients with febrile convulsions will go on to epilepsy." This contrasts with a relatively poor prognosis for various forms of organic epilepsy. The electroencephalographic patterns in febrile convulsions are generalized rather than focal, with spontaneous improvement expected as the brain matures. Children with repeated or severe febrile convulsions deserve prolonged anticonvulsant therapy, just as does any other patient with idiopathic epilepsy.

Syndromes variously designated as "nodding spasms," "salaam seizures," or "massive myoclonic epilepsy" have been clarified to a large extent (2). The seizure pattern in affected infants characteristically consists of a quick nodding or "ducking" of the head, together with sudden extension of the arms; these symptoms typically recur many times each day. The electro-

[1] This review was concluded with notes taken at the combined meeting of the American Pediatric Society, British Paediatric Association, Society for Pediatric Research, and Canadian Paediatric Society—Societé Canadienne de Pédiatrie; Quebec City, Canada, June 15–18, 1955.

[2] These include C. H. Snyder, R. H. Lennox, J. H. Arnold, E. L. Sailors, A. L. Lawing, J. P. McGovern, J. M. Horan, W. T. Newsom, and R. H. Hardie.

encephalogram typically shows huge "mountainous" arrhythmia, the so-called "hypsarrhythmia"—i.e., continuous non-rhythmic, high voltage slow waves, mixed with multiple spikes arising irregularly from all parts of the cortex, often with shifting electrical foci. This might also be considered to represent a severe form of petit mal variant, particularly because the majority of these infants show later typical paroxysms of this type. Gibbs has emphasized that this should be considered a very serious form of epilepsy, as 87 per cent of these patients become feebleminded, and nearly half of them go on to later development of typical grand mal seizures. Etiology is obscure, and treatment is notoriously unsatisfactory, though phenacemide (Phenurone) has been found occasionally effective even after failure of phenobarbital and diphenylhydantoin (Dilantin) sodium. The work of Stamps *et al.* (3) indicates that the more or less empiric administration of wide spectrum antibiotics may be effective in controlling some of these distressingly progressive patterns; this work will require further confirmation.

Serial electroencephalograms over many years in a group of children with epilepsy and focal dysrhythmias appeared to justify the conclusions that focal spike discharges in the tracings do not necessarily indicate the presence of an organic lesion in a particular area (4). There apparently are shifting foci, common in the occipital area at around four years, moving toward the central region at about nine years; many patients observed later are found to have normal electroencephalograms, or shifts from mid-temporal to anterior temporal foci; thus the finding of focal spike discharges cannot be considered an indication per se for pneumoencephalographic or surgical attack. Such studies serve to emphasize a fact not commonly enough appreciated: that the clinical and electrical manifestations of epilepsy in childhood often tend to be a function of age rather than of the nature or location of causative lesions; infants tend to show typical "hypsarrhythmia," toddlers perhaps the "petit mal variant patterns," while older children often have occipital or temporal foci—all without necessary relationship to cause of seizures or nature of the underlying disease.

In a small group of patients, synthetic diets essentially free of phenylalanine have produced rather remarkable improvement in the clinical manifestations of oligophrenia phenylpyruvica (5, 6). Armstrong & Tyler concluded that the defect in this metabolic disorder consists of an inability to oxidize phenylalanine to tyrosine, with resultant high blood levels of phenylalanine leading to the familiar neurologic manifestations directly, or from the toxicity of some other abnormal metabolic product or products of this amino acid. Administration of tyrosine without restriction of phenylalanine apparently succeeds only in darkening the hair without improving cerebral function.

As a last resort for certain children with intractable epilepsy, hemiparesis, and mental deficiency, surgical hemispherectomy has again been proposed (7 to 10). From results observed in certain cases, it would appear that when one hemisphere is severely damaged or atrophic, the other takes over nearly

all function from the diseased side, the latter then serving only as a detrimental epileptogenic area. Removal of the atrophic hemisphere has resulted in improvement of patients with epilepsy and with even some paradoxical lessening of hemiplegia and aphasia. There is also evidence to suggest some slight improvement in intelligence following this procedure. Certainly, the operation appears to have merit in management of selected intractable cases.

Encouraging additional reports have appeared attesting the usefulness of the chelating agent, calcium ethylene diamine tetra-acetate, in therapy of lead poisoning (11 to 14); though the drug may be given orally or subcutaneously, apparently the intravenous route is preferred, in dosage up to 1 gm./30 lbs. of body weight daily.

Encouraging and most intriguing effects of vitamin B_{12} in therapy of neuroblastoma or sympathicoblastoma came with Bodian's amazing finding (15) that intramuscular doses of 1,000 μg. of this substance given daily over long periods have resulted in remarkable amelioration or apparent clearing of manifestations in eight of 17 children so treated; serial biopsies of tumors during treatment have shown progressive shrinking and disappearance of primary or metastatic lesions without the evidences of maturation in tumor cells that had been the theoretic basis for the trial. The mode of action here is unknown, but certainly clinical results have been encouraging enough to demand a much more extensive experience.

Reserpine (16) has proved to have gratifying tranquillizing effects in hyperkinetic disturbed children, whether of purely emotional or organic types; the consensus seems to be that the effect of this drug in calming these patients and lengthening their attention span makes it particularly helpful in training and educational problems. Preliminary experience indicates that it now appears to be the drug of choice for reducing overactivity associated with brain injury so commonly encountered in mentally retarded children. Dosages have centered about 0.001 gm./M^2/day, given in three or four equal parts.

Poliomyelitis

The pressures, confusions, and concerns attendant on the widespread use of Salk vaccine following the Francis report (17) will not soon be forgotten by anyone who participated. Little point would be served by reviewing the evidence that still leads to conflicting reports and many official or nonofficial recommendations and modifications at this writing. Despite the setbacks encountered in 1955, we can only hope that a thoroughly-aroused public opinion will lend added impetus to early successful development of an effective and safe immunizing agent. Encouraging progress is recorded in the painstaking development of a vaccine from attenuated and avirulent strains of polio viruses, though indications now are that this preparation will not be ready for mass application very soon.

A recent brief report (18) indicates that human amniotic cells may prove to be a suitable alternative to monkey kidney cells for growth of polio

viruses. This and other proposals will require further study, but may soon lead to important modifications in methods for production of vaccines.

Studies conducted in 1953 cast doubt on the practical usefulness of gamma globulin for passive immunization against poliomyelitis, particularly as regards its common use in concomitant household exposures (19). Hammon (20) has subsequently pointed out, however, that this agent may still have usefulness, particularly in stressful situations with known or suspected exposure. An official recommendation of the American Academy of Pediatrics is: "As to care of exposed susceptibles, it is of uncertain value when given for this purpose following exposure" (21).

Shaw & Levin (22) have emphasized that there is a high incidence of paralytic manifestations to be found among patients considered earlier to have had acute nonparalytic poliomyelitis. Their study certainly appears to justify the admonition that repeated followup examinations are necessary over long periods to detect clinically important degrees of muscle weakness. With publication of this most interesting and informative report, the editor of the *Journal of Pediatrics* ingeniously and simultaneously published the solicited opinions of several experienced observers, which, in the main, agreed with this major point. In Shaw's reported experience, more than 90 per cent of all patients admitted in preparalytic stages of poliomyelitis showed detectable paralyses of some degree during their subsequent course.

The Barach "exsufflator" (23) has come into rather widespread use. The device is designed to force exsufflation by gradually inflating lungs to positive pressures of 30 or 40 mm. Hg, followed by swift pressure drops below atmospheric levels. The resultant mechanical elimination of bronchial secretions may obviate the necessity of tracheotomy in selected individuals with respiratory weakness and difficulty in clearing, including some with varying degrees of atelactesis due to this cause.

A clear and simple nomogram relating volume of tidal air to body weight and breathing frequency has been prepared by Radford *et al.* (24); this should undoubtedly soon find its way to the handbooks or pockets of those physicians directly concerned with care of patients having various patterns of bulbar and respiratory involvement.

Tuberculosis

During the year, a large scale cooperative study was initiated to evaluate the usefulness of isonicotinic acid hydrazide (INH) for preventing complications of primary infection tuberculosis among young patients. This study was a reasonably obvious aftermath of remarkable improvements observed in various forms of tuberculosis following therapeutic use of INH, particularly because at the time the study was initiated, no single report had appeared in which meningitis developed while INH was being given for any other form of tuberculosis in an infant or child. The pros and cons about such systematic drug therapy for early primary infections have been well aired (25 to 28), though it seems clear that no finally authoritative answer

can be given until the present co-operative field trial has been completed; this will probably take at least two years. Certainly, despite improvements in prognosis for erstwhile fatal forms of tuberculosis which have occurred stepwise during recent years with development and use of effective agents, much yet remains to be desired in results of treatment especially for those with meningitis (28, 29). It is attractive to believe that reasonably simple, though prolonged therapy, initiated soon after development of the primary infection, will turn out to be as effective as it seems logical.

Of apparently increasing importance is the problem of INH-resistant strains of tubercle bacilli (30 to 34). Middlebrook's extensive studies appear most pertinent, and indicate that catalase-requiring, INH-resistant organisms are relatively nonpathogenic when injected into normal guinea pigs, whereas catalase-positive, INH-susceptible strains cause typical lesions; of these latter, some are completely susceptible to INH, while others are still resistant to low levels. Pending confirmation of these observations, for details of which the reader is referred to the original work, it appears that the minimum dosage of INH employed in therapy of any tuberculous lesion should probably be in excess of 8 mg. per kg. per 24 hr. By means of cultures with sensitivity studies made twice weekly after initiation of INH therapy, Johnston & Riddell (32) demonstrated that the more frequently cultures were made, the more frequently were resistant strains encountered; they also found that while one culture might contain resistant organisms, subsequent isolations could be completely susceptible, and that organisms having low levels of resistance to INH (0.2 to 1.0 gamma per ml.) were very likely to become susceptible again, while strains resistant to higher levels (5 gamma per ml. or more) did not revert. Tompsett (33), in extensive investigations, pointed out the necessity for quantitating both the number of resistant organisms in cultures and their degree of resistance, finding that in some patients after periods of seven to nine months of INH therapy as many as 70 per cent of organisms recovered in cultures were still completely susceptible, when it might be assumed that by this time they would be either dead or completely resistant. Sweetnam & Murphy (34) have suggested that INH-resistant organisms develop mainly in large necrotic tuberculous lesions, but not commonly in smaller foci more characteristic of tuberculosis during childhood; perhaps it is easier for INH to reach and affect organisms in such younger and smaller lesions, so that the hazard of developing resistant strains of tubercle bacilli may be relatively small in most infants and children as contrasted with adults.

Additional antituberculous drugs are being developed, and two of these at present deserve particular mention. Brodhage (35) found that the para-aminosalicylic acid salt of INH had a greater tuberculostatic effect than did an equal mixture of the two constituents; interestingly also, he found that bacilli resistant *in vitro* to both PAS and INH were sensitive to the salt. In a small clinical study, Payne *et al.* (36) found that patients treated with a streptomycin salt of INH alone appeared to develop resistance to both

INH and streptomycin. Additional reports dealing with use of such compounds will be awaited with interest.

The auditory deficits following streptomycin and dihydrostreptomycin therapy have again been studied by Oldham (37); he found an increased proportion of patients with hearing loss among those who were treated for meningitis with both streptomycin and dihydrostreptomycin as contrasted with the proportion affected when the same total dose of either agent was given alone.

Two interesting monographs have appeared, one by Bentley *et al.* (38) presenting observations from a prolonged study of a large group of tuberculous children, the other by Irvine (39), compactly but comprehensively dealing with BCG and Vole vaccines.

Rheumatic Fever

It is estimated that 50 per cent of rheumatic heart disease is preventable (40); among persons with group A beta hemolytic streptococcal infections, 80 per cent have acute respiratory symptoms, and about 3 per cent develop rheumatic fever. Immediate and adequate penicillin therapy is usually effective in preventing the latter. A committee of the American Heart Association has recommended that all persons who have had an attack of rheumatic fever receive continuous prophylaxis with sulfadiazine or penicillin, starting early and continuing until age 18; adults should be treated for at least five years following the latest attack. Recent studies have demonstrated the efficacy of long acting repository penicillin, both in eliminating group A streptococci from resistant carriers and in prophylaxis of rheumatic attacks (41); detectable blood levels have been maintained as long as 28 days after a single injection of 1.2 million units of one preparation. Among 96 rheumatic subjects, of whom 75 were followed for six months or longer, there were no clinically recognizable recurrences among those whose rheumatic activity was quiescent when prophylaxis was started (42); two patients had significant rises in antistreptolysin 0 titer, and one had a mild rheumatic recurrence following a positive culture. There were only four positive cultures among more than 1000 taken after start of treatment.

Controversies continue over the relative virtues of hormone therapy, enthusiasm being tempered by lack of adequate well controlled followup data. Though early clinical results indicate that salicylates, cortisone, and ACTH are reasonably comparable in efficacy (43), it is possible that cortisone may have a slight advantage in terms of residual cardiac damage. Several authors (44, 45) leave the impression that initiation of cortisone in large doses within a week of onset, and continued over long periods, has been followed by disappearance of murmurs in a higher proportion of patients than would otherwise be expected—94 per cent or more. In most clinics, cortisone is considered a life-saving therapeutic agent in some patients with clinically severe and obviously progressive disease.

Illingworth *et al.* (46) administered large doses of sodium salicylate de-

signed to achieve blood levels of 30 to 40 mg. per 100 ml.; they studied 27 patients under this regimen together with a control group of 28 individuals. Falls in temperature and sedimentation rate were significantly faster in the salicylate-treated group. While other differences were not particularly significant, it was noted that in the salicylate group fewer patients developed nodules, relapses, apical diastolic murmurs or increase in systolic murmurs, and that fewer of the treated patients demonstrated cardiac involvement in later follow-up examinations. From the same clinic (47), further studies were reported, assigning rheumatic patients to three treatment groups: high salicylate plus cortisone, high salicylate alone, and low salicylate alone. The sedimentation rate fell most rapidly in the first group, returning to normal in more than a third of them by the end of a week; similar falls were recognized in the other two groups only in about 12 per cent. For group 1, the usual number of days required for the sedimentation rate to become normal was 17, contrasting with 39 and 50 days for groups 2 and 3 respectively.

In four patients with acute rheumatic manifestations (48), aspirin was found to increase metabolism despite reduction of fever; ordinary doses of acetylsalicylic acid or of sodium salicylate produced 11 to 12 per cent increases in oxygen consumption. Smith and others (49) found that urinary excretion of adrenocortical steroids was normal during administration of salicylates, as contrasted with the elevated levels during hormone therapy, a point against an "ACTH-like" effect of salicylates.

Experience with a large group of patients (50) led to the conclusion that antihyaluronidase and antistreptolysin titers were about equally sensitive indicators of immunization by hemolytic streptococci, though response of the two antibodies was not correlated, thus affirming the justification for employing both tests simultaneously. Eight per cent of patients with acute rheumatic fever failed to show definitely elevated titers of either, but five per cent of those with questionable elevations had significant drops with recovery.

There have been inconclusive speculations regarding antistreptolysin S, a naturally occurring, ether-extractable, highly unstable compound resembling a lipoprotein, which is present regardless of previous streptococcal contact (51); there is a quantitative relationship between S-inhibitor and serum phospholipid E, which is known to be diminished in fever and in persons who are susceptible to rheumatic fever. Investigations of serum and plasma vitamin A levels (52, 53) have shown them to be reduced during acute rheumatic fever, but also during pyrexia of any cause, or during periods of poor intake.

A latent hemolytic mechanism may be present in acute rheumatic fever; red cell survival times, measured by the Ashby technique, were abnormal in eight patients studied (54).

Ballistocardiograms (64 in 18 young adults with acute rheumatic fever) were mildly abnormal in two patients, so these are not particularly useful

in this disease; measurement of cardiac output in patients with chronic rheumatic heart disease showed an abnormally increased difference in A-V oxygen content and inability to increase cardiac output with exercise (55, 55a).

Congenital Heart Disease

Major interest in this field has centered on new surgical technique and refined diagnostic maneuvers (56).

Using cross circulation, with a donor (usually a parent) furnishing oxygenated blood during exclusion of the defective heart, cardiotomy and direct suturing of ventricular septal defects has been accomplished by Lillehei and his group in 24 of 31 patients, all of whom were selected for the procedure on the basis of severe and progressive symptomatology indicating a very poor prognosis. Three of six patients have survived complete repair of tetralogy (trimming of infundibular stenosis and repair of septal defect) by the same technique. The main criticism of the procedure obviously arises from the standpoint of risk to donors; so far, however, these workers have reported only two significant reactions. Reports of further applications are surely to be anticipated, together with other devices for accomplishing cross circulation to attain the same ends.

Encouraging successes have been achieved in surgical correction of atrial septal defects. Employing hypothermia for open cardiotomy, Swan had only two operative deaths and remarkable changes in the others; complete closure of the defect was demonstrated in 17 of 19 patients who were studied by cardiac catheterization postoperatively (56). Additional reports have been made dealing with invagination of the atrial wall to close the defect, indicating conspicuous successes among those with persistent ostium secundum, but much poorer results in those with the lower ostium primum. The "well" technique has been employed in an additional group of patients operated on at the Mayo Clinic for atrial defects, with excellent results reported in 29 of 33 patients. From Copenhagen, Sondegaard has proposed an ingenious and apparently effective method for closure of atrial septal defects, in which a heavy suture is led in the path of a probe advanced through the inter-atrial sulcus; by this procedure, the entire atrial septum is encircled, following which the suture is drawn taut to obliterate the defect (56).

Taussig has reported on the first 414 pulmonary-systemic artery anastomoses done for cyanotic heart disease, especially tetralogy. Followup on the first 100 shunts performed (six to eight years ago) has indicated that good results were secured in 68, fair in 16, poor in two, and that nine patients died during surgery and five after discharge (56).

The variations and prognostic significance of the clinical picture associated with pulmonary hypertension accompanying patent ductus arteriosus have been elucidated (57); characteristically, physical findings of children with severe pulmonary hypertension include extremely loud and split pulmonary second sounds, absence or variability of the continuous murmur

otherwise characteristic with patent ductus arteriosus, and conspicuous growth retardation. Conventional studies show moderate to marked cardiac enlargement by x-ray, and electrocardiographic evidences of right ventricular hypertrophy; calculations following catheterizations have shown that the pulmonary blood flow roughly parallels pressure differences between the two circulations (i.e., minimal increase in pulmonary flow with severe pulmonary hypertension). Such evidences justify a relatively poor prognosis for successful surgical correction of patent ductus arteriosus.

Hemoglobins

During the past six years, since Pauling's electrophoretic differentiation of the hemoglobin in sickle cells (58), a number of additional abnormal hemoglobins have been reported. Confusion in terminology later led to an attempt at standardization of nomenclature during a symposium held by the Hematology Section of the National Institutes of Health (59). Table I sets forth the recommended as opposed to the old symbols; it was suggested that new hemoglobins be assigned the next letters available in the alphabet in the order of their discovery. Since this proposal, at least three new hemoglobins have been discovered, E, G, and H (62, 63, 64). Any combination of pathologic hemoglobins results in hemolytic anemia, but if one is heterozygous with normal hemoglobin, then an asymptomatic nonanemic trait or carrier state will occur. An excellent summary of the clinical and hematologic characteristics of the various hemoglobin combinations is contained in a review by Singer (65). The occurrence of hemoglobin variants appears to be genetically controlled, the determinants for abnormal types being alleles of the genes for normal hemoglobin A. Specific genetic patterns for G and H have not been established, though from limited observations it appears that the pattern for H may be unlike the others: two subjects were encountered in a Chinese family with both parents having normal hemoglobins. The observation that hemoglobin F appears inconstantly but in considerable amounts in homozygous as well as double heterozygous states has caused speculation that its production may also be controlled by genes which are not alleles of hemoglobin A. Neel and Pauling (66, 67) have speculated that the thalassemia gene is allelomorphic with these two hemoglobins.

TABLE I

Terminology of Hemoglobins

	Recommended	Old
1. Normal adult hemoglobin	A	N, a
2. Fetal hemoglobin	F	f
3. Sickle cell hemoglobin	S	b
4. Hemoglobin C (60)	C	c,III,X
5. Hemoglobin D (61)	D	d

For practical purposes these hemoglobins can be differentiated with relative ease by filter paper electrophoresis, though resistance of fetal hemoglobin to denaturation with alkali may also be useful in distinguishing it from the normal adult type. Employing a simple qualitative technic, Apt & Downey (68) adapted this latter procedure for distinguishing between melena from swallowed maternal blood and that due to gastrointestinal hemorrhage in newborns.

Allergy

Black's third edition of Vaughan's *Practice of Allergy* includes much new and revised material of interest (69). There are also two comprehensive monographs emphasizing current trends in therapy of allergic disease in children (70, 71). Of particular interest was work showing that bacterial products secured from eczematous lesions will produce positive homologous patch tests (72).

Continued interest and several investigations have led to refinement and better application of steroid therapy in allergic states. Perhaps most dramatic have been results reported in relief of status asthmaticus (73), particularly among those failing to respond to older, more conservative measures. Locally, hydrocortisone acetate ointments in 104 patients with eczema yielded results "from 75 per cent to 100 per cent effective when used in an appropriate base." Others have reported good results with topical hydrocortisone is this connection (74, 75), and also with the more recently tested and apparently more potent fluoro-hydrocortisone (76). Warning about dangers of steroid therapy and advising limitation of its use over prolonged periods, O'Keefe (77) has stressed the benefits to be secured with "combined cortisone and desensitization" in infantile eczema. Including eight patients with severe asthma or eczema among a larger group with other conditions treated with cortisone over periods of from six months to four years, Blodgett *et al.* (78) concluded that temporary suppression of growth and maturation under cortisone therapy does not necessarily contraindicate its careful administration over considerable periods of time in treatment of conditions likely to be benefited by it. They found rather remarkable variations in the dose of cortisone needed to produce reduction in growth rate; this was greatest, up to 250 mg/M²/day, in allergic infants; when dosages were reduced or discontinued, the trend was for rate of growth and maturation to increase toward or above pretreatment levels. As a result, many patients "were able to regain during periods when therapy was reduced or discontinued much of the ground lost while on treatment."

Topical hydrocortisone has apparently provided rapid and prolonged nasal decongestion without undue rebound in symptomatic management of hayfever, resistant to more conventional measures; again the dangers of steroid therapy in this situation have been stressed (79, 80). The interval, over which hypofunction of the adrenal glands may occur in stressful situa-

tions following discontinuance of steroid therapy, must be extremely variable (81, 82); it has been proposed that patients exposed to stress, and who have previously had cortisone therapy at any time during the past year, should have replacement therapy.

The matter of prophylaxis by carefully selective feeding for potentially allergic newborns has been reconsidered by Glaser & Johnstone (83, 84, 85), leading to a recommendation that soybean products should be substituted for cow's milk in this situation. Following such substitution, they felt they had prevented not only the development of allergy to cow's milk but had also appreciably reduced the frequency of other allergic disorders in later infancy and childhood. Ratner *et al.* (86) found that orange juice protein does not readily cross the gastrointestinal barrier, and perhaps only in rare instances is it responsible for allergic manifestations. The importance of food allergy as a cause of infantile diarrhea has again been stressed by a report of 36 patients, 11 having reasonably typical manifestations of the celiac syndrome, apparently due to this cause (87).

Though "hen or egg" considerations might be invoked, the specific role of psychologic foundation or overlay in many apparently allergic disorders continues to be of interest. Particularly as to asthmatics (88, 89), the dominant parent who refuses to permit the child normal channels for release of tensions is singled out. The importance of emotional disturbances in either parent or child serving as trigger mechanisms for initiating basically allergic symptoms has been repeatedly emphasized (70, 90), encouraging therapy directed toward relief of tensions and anxieties affecting parent-child relationships after the individual problem has been considered "to gain proper perspective in each case" (91). Certainly, the evidences are accumulating that allergic disorders, like most symptoms or diseases, result from the sum total of multiple forces (92, 93).

Defective hearing, apparently allergic in cause, and improved with use of antihistaminics, has been described by Armstrong, who employs a simple quantitative audiologic test in study of such patients (94, 95). Reserpine has been reported to produce excellent symptomatic improvements in various dermatoses, many of which were considered atopic (96, 97). With use of insect-extracts in hyposensitization, relief might be afforded to patients who have severe reactions to wasp or bee stings (98); this reference lists commercial sources for such extracts.

Rounds (99) has recently emphasized adverse effects of aminophylline related to dosage, routes of administration, and individual idiosyncrasies. He points out that the smallest suppository preparation commercially available represents probably an excessive dose for individuals weighing less than 75 pounds. The clinical picture of aminophylline poisoning resembles that of hypertensive encephalopathy as occasionally seen with acute nephritis; a number of deaths have been attributed to its use, particularly when given intravenously.

Renal Disease

A retrospective study of more than 1300 records of patients with the nephrotic syndrome has indicated an improved outlook for these children, particularly with planned therapy employing adrenocortical-active hormones. Comparing modified life tables prepared for three groups of patients—no hormone therapy, hormones only for relief of edema, and "predetermined plans" of therapy given without regard to status of edema—Riley (100) found a significant reduction from the expected number of deaths in the latter group. Careful attention to time-dose relationships is important for maximal benefits; for ACTH doses are usually from 150 to 200 mg. per M^2, and for cortisone 350 to 500 mg./M^2 divided into three or four equal doses daily (101). Criteria defining various end-points for initial or repeated courses of therapy consist mainly in return to a normal sedimentation rate, cessation of proteinuria, or return to normal electrophoretic patterns of plasma proteins; using these same criteria, repeated courses are given when the sedimentation rate rises, proteinuria reappears, or the A/G pattern becomes less normal (100). Such intensive therapy, given in initial courses usually of from eighteen days to four weeks, and repeated as often as indicated by symptoms or laboratory criteria of relapse, has kept the disease in an apparently arrested state for a majority so treated. A bad prognosis may be predicted by a poor response to the initial course, particularly when the proteinuria fails to clear, or the sedimentation rate or blood pressure to fall, within 18 days. There seems no doubt that relapses are less frequent with such prolonged or repeated courses (102 to 106), though observations have not yet continued long enough to prove that eventual mortality rates are affected (107).

Observed and expected changes occurring with diuresis include increases in glomerular filtration rate (102, 108), serum complement (104, 109, 110, 111), and serum albumin (112, 113); decrease in salt-retaining substances in urine (114, 115, 116), in antidiuretic activity of blood (114, 115, 116) and urine (117), and in glomerular permeability to albumin (117, 118); and return toward normal excretion of sodium and potassium (119, 120). Hypoelectrolytemia, convulsions, and increased risk of infections constitute the major hazards of hormone therapy (105, 121, 122, 123). Impaired renal function or sustained hypertension probably contraindicate prolonged or repeated courses (123).

Symptomatic results of therapy with dextrans for control of edema, ascites, and anasarca have not been fully established (123); they may be useful occasionally alone (124 to 127), or in combination with hormones (105); complications to their use include occasional bleeding tendencies and anaphylactoid reactions (124, 128 to 131).

Interest continues in evaluation of hypotensive agents useful for control of acute hypertension in nephritis. Magnesium sulfate has been re-evaluated, particularly from the standpoint of its effects on renal function (132). Given intravenously to produce serum levels of more than 5 mg. per cent

in acute hypertensive phases of nephritis, it increases glomerular filtration rate and renal plasma flow, and decreases the filtration fraction. Though reported experience with alkavervir (Veriloid) are encouraging (133), it remains to be seen whether its antidiuretic effect and the decrease in glomerular filtration rate it produces in adults with essential hypertension are significant in children (134, 135); clinically, it does not appear to accentuate renal damage nor to reduce cerebral blood flow (136, 137). While hydralazine (Apresoline) frequently reduces blood pressure, it usually also reduces glomerular filtration rate and urine flow (138, 139). The most recent contribution, from Etteldorf & Smith (140), reports advantages from combining reserpine in doses of .07 mg. per kilogram intramuscularly with small amounts of hydralazine hydrochloride—0.1 to 0.15 mg. per kg.; this resulted in a prompt and prolonged relief of hypertension. In seven patients observed, a single dose of this combination produced satisfactory hypotensive responses for from ten to seventy-two hours. There were slight increases in renal plasma flow, no change or slight decreases in glomerular filtration rate, and filtration fractions remained within normal limits while urinary flow decreased during clearance periods. Others have observed similar gratifying results with this combination in varying dosages.

After reviewing many reports on hypertension in nephritis, one gains the impression that there must be a good deal of variation in results related to the type of experiment, stage of the disease, and various criteria employed for evaluation. Certainly, it is common clinical experience to find that, although one drug fails for a given patient on one occasion, it may succeed at another time or for another patient. Also, it seems clear that important changes in renal function are not always directly related to apparent clinical response, and finally each of the drugs evaluated or used may produce undesirable side effects, in part inseparable from desired therapeutic action (132, 133, 135, 136, 138, 141).

Aortography with sodium acetrizoate (Urokon) or iodopyracet (Diodrast) has been useful in delineation of anomalous renal arteries and localization of pheochromocytoma (142, 143, 144), in the study of unexplained hypertension or hematuria (145), and in preoperative evaluation of the degree of parenchymal damage in certain cases of hydronephrosis (146). The translumbar route of injection ordinarily employed in adults is technically more difficult in children (147), so that retrograde injections via the femoral artery seem to be at present the preferred technique for filling the renal arterial system (148). Though the procedure certainly carries risks of direct or indirect trauma, idiosyncrasy, or neurogenic reactions, it can be useful in objective study of selected cases (149, 150).

Though enough evidence has accumulated to indicate that needle biopsy of the kidney is a relatively safe procedure and a helpful diagnostic tool in skilled hands (151, 152, 153), only a few reports have dealt with the procedure in children, these being included among larger series of adults (154). Obviously, it has a large place in experimental study of renal disease in

humans (155, 156) and in animals (157). Its hazards should be fully understood by anyone interested in undertaking it; these have been well described (158, 159).

Careful study of specific renal tubular dysfunction has thrown additional light on the pathogenesis of some rare nephropathies (160, 161). Latner & Bernard, for example, have shown that infants with idiopathic hyperchloremic renal acidosis are as capable of increasing ammonia production and titratable acidity in response to phosphate infusions as are otherwise normal acidotic controls (162); these workers postulate an abnormal reabsorption of bicarbonate in the proximal renal tubule, with flooding of the distal tubular mechanism. Smith & Schreiner (163), working with adults in hyperchloremic renal acidosis, found no evidence of further flooding by bicarbonate infusion, and feel that both proximal and distal tubular defects are present.

Further light has been shed on another of the unusual nephropathies, the Fanconi-Lignac syndrome (164). Nephron dissection has shown an elongation of the convoluted tubule as it leaves the glomerulus (165), and special stains have shown an absence of alkaline phosphatase in the tubular cells (166); both findings emphasize the possibility that this is a primary renal tubule disease.

Newborn and Premature

Since most workers continue to report leading neonatal mortality problems as being related to pulmonary physiology (167), advances in basic knowledge in this area are of great interest. Smith and co-workers (168) studied newborn infants manifesting respiratory distress and cyanosis clinically characteristic of "the hyaline membrane syndrome" or "congestive pulmonary failure" and found that such infants had normal tidal volumes, alveolar ventilation, and approximately normal carbon dioxide production. In a group of 20 there were five deaths, each at autopsy having major pulmonary lesions. Of particular interest, it was found that physiologic data in the infants who died with pulmonary lesions were not strikingly different from those who recovered.

The opinions of many authorities concerning "resuscitation" of newborns have been extensively reviewed (169, 170, 171). Apgar found no significant correlation between levels of blood oxygen content, measured in the first three hours after birth, and intelligence as gauged by Stanford-Binet tests later in childhood (171). Further studies on the care of infants delivered by cesarean section have again suggested routine gastric suction in this situation in order to minimize respiratory complications (172). Important clarification of the pathologic picture of pulmonary hyaline-like membranes has resulted from the work of Anderson (173, 174) and Gellis (175). Gilmer & Hand have contributed further information regarding composition of hyaline membranes, and have reported important studies related to the specific histologic location of the hyaline material beneath the epithelial

lining of the air spaces (176); the existence of this lining itself has been denied by many.

Extensive studies in hemolytic disease have further clarified and defined many specific problems related to that type associated with ABO incompatabilities (177 to 180). Biochemical studies of erythroblastotic infants have demonstrated that they have a remarkably effective homeostatic ability for adjusting to stresses inherent in exchange transfusions (181, 182, 183). Studies on the mechanism for production of kernicterus have further implicated excessively high serum levels of bilirubin as a direct etiologic factor (184, 185, 186). One report suggests that perhaps hyperbilirubinemia of "physiologic" jaundice may occasionally be related to production of kernicterus among otherwise normal newborn infants (187). Even though kernicterus associated with hemolytic disease may be virtually eliminated through skillful exchange transfusions, there remains the possibility of an increased incidence of mental retardation or other central nervous system disorder as a complication of this disease. Preliminary studies (188, 189) seem to indicate that significant mental retardation among these infants who survive may, indeed, be only slightly increased beyond that otherwise expected. Unless severe, signs of central nervous system damage among these babies in the newborn period are apparently not highly reliable for prognosis (189).

Although generally ranked in fourth place among anatomic explanations for neonatal death, infections remain of primary importance, since with our limited present knowledge, these seem most susceptible to direct prophylaxis. Stoppelman (190) has reported a bacteriological survey defining establishment of nasopharyngeal flora in premature infants with and without "prophylactic" administration of antibiotics. No significant differences in the bacterial flora were noted between infants born at home or other hospitals and subsequently admitted to the study hospital, and those delivered and maintained in a different nursery at the study hospital. Seventy per cent of all cultures obtained from these infants on the first day remained sterile. Streptococci were significantly reduced in nasopharyngeal flora from those receiving antibiotics. Of interest in this connection also, Dancis & Kunz (191) found from serial *in vitro* tests that early bacteriostatic activity against *E. coli*, *N. catarrhalis*, and *S. derby* dropped off during the first few weeks but was usually present again around one year. The addition of gamma globulin enhanced the bacteriostatic activity of premature infant serum, indicating that a deficiency of this fraction is at least partially responsible for their poor bacteriostatic performance. Of epidemiologic importance in nurseries have been further observations by Neter and Weintraub (192) as to relative frequency of "pathogenic" organisms recovered from infants with and without signs of illness.

The role of excessive oxygen in retrolental fibroplasia has been further elucidated through a number of experiments and clinical observations (193 to 197), particularly those of Patz (198), Zacharias (199), and, of course,

humans (155, 156) and in animals (157). Its hazards should be fully understood by anyone interested in undertaking it; these have been well described (158, 159).

Careful study of specific renal tubular dysfunction has thrown additional light on the pathogenesis of some rare nephropathies (160, 161). Latner & Bernard, for example, have shown that infants with idiopathic hyperchloremic renal acidosis are as capable of increasing ammonia production and titratable acidity in response to phosphate infusions as are otherwise normal acidotic controls (162); these workers postulate an abnormal reabsorption of bicarbonate in the proximal renal tubule, with flooding of the distal tubular mechanism. Smith & Schreiner (163), working with adults in hyperchloremic renal acidosis, found no evidence of further flooding by bicarbonate infusion, and feel that both proximal and distal tubular defects are present.

Further light has been shed on another of the unusual nephropathies, the Fanconi-Lignac syndrome (164). Nephron dissection has shown an elongation of the convoluted tubule as it leaves the glomerulus (165), and special stains have shown an absence of alkaline phosphatase in the tubular cells (166); both findings emphasize the possibility that this is a primary renal tubule disease.

Newborn and Premature

Since most workers continue to report leading neonatal mortality problems as being related to pulmonary physiology (167), advances in basic knowledge in this area are of great interest. Smith and co-workers (168) studied newborn infants manifesting respiratory distress and cyanosis clinically characteristic of "the hyaline membrane syndrome" or "congestive pulmonary failure" and found that such infants had normal tidal volumes, alveolar ventilation, and approximately normal carbon dioxide production. In a group of 20 there were five deaths, each at autopsy having major pulmonary lesions. Of particular interest, it was found that physiologic data in the infants who died with pulmonary lesions were not strikingly different from those who recovered.

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the large cooperative study conducted under the auspices of the Kresge Eye Institute (200). Ingram & Ker (201) have demonstrated a significant association between retrolental fibroplasia and cerebral palsy by means of a followup survey. A field study of retrolental fibroplasia in relation to specific hospital standards of practice (202) has served to stimulate a healthy interest in more critical periodic evaluation of care techniques, regardless of how "logical or conventional" they may seem. There has been relatively little reported recently concerning nutrition of newborns. Several improvements were described in the technique of feeding weak and debilitated premature infants by means of indwelling plastic tubes (203, 204, 205). Some preliminary investigations have revealed variations in the electrolyte pattern among infants fed on diets varying widely in electrolyte, protein, fat and carbohydrate composition (206 to 210). An important feature of these studies has been to emphasize the clinical importance of a variety of manifestations centering about immature renal functions in premature infants.

An intriguing report by Åkerrén (211) dealt with the peculiar characteristic physiognomy observed in infants of diabetic mothers, which aptly merits the designation "tomato-face"; with this, he reviewed the decisive endocrinologic disturbances which lead to such a striking Cushingoid habitus.

Correlating with body weight, values for uropepsinogen excretion may have merit as an additional critical index of maturity; excretion seems to be relatively independent of protein intake, and successive increases were observed in small premature infants during the first month of life (212).

Infectious Disease

Careful observation and sensible speculation characterize a report by Capps and others (213) dealing with an outbreak of hepatitis in an orphanage; apparently, though clinical manifestations differ somewhat in this very young age group, infectious hepatitis is probably far more prevalent than has been recognized. Manifestations are usually protean over a period of from three to 24 weeks; in a sample of 36 infants and toddlers with convincing evidences of hepatitis, the conspicuous features consisted in objective laboratory findings of disturbed liver function, a surprisingly small proportion having conspicuous enlargement or tenderness of the liver. Nonicteric forms are common, and only a small percentage of these progress unfavorably. Meticulous attention to techniques for avoiding the typhoidal type of transmission is stressed in prophylaxis (214).

Apparently the entire gamut of clinical symptomatology for pulmonary disease may be present in children with interstitial cell pneumonitis; this has been noted particularly in institutionalized and small, dystrophic infants between six weeks and four months of age (215, 216). Though etiology is obscure, pathologic features are reasonably typical, consisting in the main of widespread interstitial infiltration by large mononuclear cells which resemble plasma cells. Onset is characteristically insidious, but with progres-

sive severe dyspnea; roentgenograms typically show a milky opacity extending bilaterally from the hilar areas. There appears to be no specific benefit from antibacterial agents, and therapy is largely supportive. From Finland, followup studies have suggested that possibly permanent sequelae may consist of faulty mental and physical growth in a few patients accompanied by unexplained progressively rising levels of plasma calcium and nonprotein-nitrogen, with delayed bone growth and some osteosclerosis (217).

Among 105 examples of cytomegalic inclusion disease so far reported, all but nine have occurred in infants and small children (218). Typical manifestations in the newborn suggest severe erythroblastosis or sepsis, but evidence for isoimmunization or bacteriologic infection is absent. Though attempts to isolate an etiologic agent have been unsuccessful, a demonstration of typical inclusions in the urinary sediment is considered diagnostic. There is no specific therapeutic agent, and no convincing evidence that the disease is modified by administration of cortisone, gamma globulin, or a variety of antibiotics.

From Jerusalem came a report dealing with several cases of ornithosis in small children, serving to illustrate remarkable variations in severity of clinical manifestations (219).

Further reports attest the importance of *E. coli* serogroups, particularly 0111, 055, and 0127, related to diarrheal disease in early infancy; most strains so far reported have apparently been susceptible to one or several of the broad-spectrum antibiotics. Using *E. coli* 0127: B 8 as the etiologic tracer, Stulberg & Zuelzer (220) followed the clinical, bacteriologic, and serologic features of a nursery outbreak involving 60 infants over a period of four months; neomycin was promptly effective, and when it was given simultaneously to all infants in the nursery, the epidemic was controlled. Netter *et al.* studied the distribution of enteropathogenic *E. coli* 0111, 055, 026-hemagglutinins in random sera from subjects of different ages; they found that placental transfer from mothers to infants was slight, that titers were positive in 5 to 13 per cent of sera of infants under three months, 38 to 49 per cent between three and 12 months, 67 to 76 per cent between one and 12 years, and 93 to 98 per cent from older children and adults. Conventional bacterial agglutination tests were relatively insensitive (221). Wheeler and Wainerman have emphasized the chronicity and high recurrence rate, with numerous cross-infections, which characterize most of the outbreaks reported (222). They and others (223) remarked on the problems posed by a high frequency of asymptomatic carriers.

In New York over a period of five years, more than 300,000 doses of gamma globulin were distributed for prevention or modification of measles among preschool children; so far as could be determined, there was only one example of post-measles encephalitis in this group, this occurring in a child already suffering from cerebral palsy (224). From more than 115,000 cases of measles during this period, the over-all incidence of complicating encephalitis was considered to be 0.14 per cent; though the frequency of this com-

plication was highest among the older children, fatality rates were highest in those under five years of age. Comparing the clinical course of established encephalitis in 51 patients treated with gamma globulin with that for 108 untreated, it was concluded that this agent had no value in therapy, once the complication had developed (224).

Employing familiar electrocardiographic criteria, Goldfield, Boyer, and Weinstein found that about 20 per cent of children hospitalized for measles developed transient myocarditis; surprisingly, the incidence of myocarditis appeared to be greatest among those who had otherwise uncomplicated measles. There was no observed correlation with age or clinical severity of the measles, and apparently no permanent sequelae (225).

Clinical features quite typical of acute staphylococcal food poisoning, with considerable variations in the pathologic picture of pseudomembranous enterocolitis, have been reported in a number of children treated with broad-spectrum antibiotics for various valid indications. Cramer & Rossi (226) encountered five instances complicating apparently satisfactory response five to 10 days after initiating therapy for several common infections. From a careful clinical and pathologic study of 10 cases, Beatty and Hawes have elucidated typical features. Apparently as a consequence of effective antibiotic action, resistant-toxin-producing staphylococci "take over" to cause the acute frequently fulminating micrococcic enterocolitis in all stages from simple hyperemia through to pseudomembranes composed of epithelial degeneration over the denuded mucosae (227).

Though the syndrome of acute aseptic meningitis can probably be attributed to many causes, Sven Gard reports that Coxsackie virus B-3 is at present a conspicuous factor, at least in Sweden (228).

The subject of subdural collections complicating bacterial meningitis has been thoroughly reviewed by Smith (229), with particular emphasis on pathogenesis, clinical manifestations, and management of this lesion.

Increasing experience has led to emergence of at least three patterns relating to varying deficits in circulating gamma globulin; all are characterized clinically by repeated and severe bacterial infections, with levels of gamma globulin significantly below the normal range of 600 to 1200 mg. per 100 ml. The first, congenital aggammaglobulinemia, may be transmitted like hemophilia as a sex-linked recessive, these patients usually having gamma globulin levels below 25 mg. per 100 ml., no detectable alpha or beta isohemagglutinins, and sometimes cyclic neutropenia. Therapy with pooled gamma globulin in the amounts of 0.1 gm. per kg. per month intramuscularly is usually effective for prevention of otherwise frequent and severe infections. The acquired (adult) type occurs in either sex, with bronchiectasis and intestinal symptoms suggestive of sprue or ulcerative colitis as the conspicuous clinical manifestations; values for gamma globulin in the few patients of this group so far studied fall usually between 25 and 75 mg. per 100 ml. The third type, transient or physiologic, is apparently simply an accentuation of normal inadequacy of gamma globulin synthesis expected

in the first few months of life—a delay in "catching up" with degradation—again raising the question as to the advisability of using gamma globulin routinely as a general prophylactic measure in newborns during the first month of life (230). Janeway & Gitlin have emphasized and justified their preference for immunochemical procedures over much less accurate electrophoretic techniques in proper diagnostic study of such patients. Certainly, it should be widely appreciated that the absolute level of gamma globulin in any individual at any particular time does not necessarily reflect the type or amount of any specific antibody; therein lies the advantage of using pooled gamma globulins, at least theoretically furnishing a more complete set of antibodies than would gamma globulin obtained from a single donor. By the same token, patients with these deficiencies should be protected against infections and treated promptly with adequate antibiotics when they occur.

Finally, a new journal should be called to the attention of readers of this chapter; the first issue of *Journal of Tropical Pediatrics* appeared in June, 1955 (231). Judged from the contents of the first issue, which appeared just as this review was completed, its publication will have great appeal, particularly to physicians working in tropical and sub-tropical areas.

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DISEASES OF THE NERVOUS SYSTEM[1,2]

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Diagnosis and Localization of Intracranial Lesions

Improvement in the maneuvers available to clinicians for diagnosis of focal intracranial disease has been in recent years largely in the fields of (*a*) angiography and (*b*) radioisotopes.

Angiography.—In the first category, a more extensive use of serial films and special views to depict the arterial, capillary, and venous portions of the vascular tree has increased the usefulness of the method. A study of profusely illustrated works is necessary to appreciate its utility; hence we shall not discuss it here. Among the best reproductions of roentgen films are those in the book of Krayenbühl & Richter, *Die zerebrale Angiographie* (1). These speak effectively even if one doesn't read German. The recent book of Ecker & Riemenschneider (2) is one of the best illustrated works with an English text.

Chemical and radioisotopic aids to diagnosis.—Search for a means of identifying intracranial tumors by spotting chemical substances tending to concentrate in them began with studies with dyes. The brain was a logical place to explore, since Duran-Reynals (3) found in normal and tumor-bearing animals that the only tissues impervious to the dye Evans blue were normal brain and cord and necrotic tumor, whereas sarcomas and carcinomas localized this dye. However, in man, Sweet (4) found that Evans blue not only failed to aid identification of glioblastomatous tissue, but also that 150 mg. given intravenously stained the patient's skin a strikingly unattractive pastel shade of blue which took several months to fade out. Sorsby, Wright & Elkeles (5) likewise obtained no useful staining of gliomas with Kiton fast green V. A little early encouragement experienced by Grant (6) with Nile blue sulphate appears not to have been sustained in later cases.

Localization of lesions at operation.—Moore (7) was the first to find both a substance which would concentrate in brain tumors and a practical means of detecting it. One gram of fluorescein injected intravenously concentrated sufficiently so that Moore *et al.* (8) could distinguish normal from neoplastic brain tissue at operation by fluorescence of biopsy material inspected at once under ultraviolet light. Using this technique, Moore, Hunter & Hubbard (9) correctly diagnosed the presence of tumor in 105 of 112 cases, and erroneously made a positive diagnosis of tumor in only two of 29 cases in which it was

[1] The survey of literature pertaining to this review was concluded in October, 1955.

[2] The following abbreviations are used in this chapter: RIHSA (radioactive iodinated human serum albumin); PCG (positrocephalogram); AGG (asymmetrogammagram); CSF (cerebrospinal fluid).

absent. The surgeon could thereby determine not only when he had encountered subcortical tumor, but also, by directing the ultraviolet light into the area remaining after removal of tumor, he could spot fluorescing remnants of neoplasm not otherwise detectable. The dose of dye used produces yellow staining of the skin for but a few days. A useful degree of fluorescence does not appear until perhaps an hour after the injection, becomes maximal at two hours, and has clearly begun to fade by five hours.

Development of another method for localizing and identifying tumor at craniotomy occurred when it was found independently by workers at Harvard and the University of Wisconsin that the normally present phosphate ion labeled with P^{32} entered tumor much more rapidly than normal brain. The ratios, tumor:normal white matter, vary from about one in slow growing gliomas to over 100 in some portions of rapidly growing tumors. Moreover, these high ratios persist for many hours following the intravenous injection. Following up this observation, the group in Boston have used the delicate probe-type Geiger-Mueller counter developed by Robinson & Peterson (10) to locate and estimate the size of subcortical tumors exposed at operation. The probing portion of the counter has been reduced to a diameter of 2 mm., a size which rarely causes troublesome deep hemorrhage upon insertion into a vascular tumor. Only about one centimeter of the length of the probe near its tip is sensitive to the beta particles which are the sole radiation of the decaying P^{32}. These particles, with a maximal energy of 1.69 Mev, have a maximal penetration of brain tissue of circa 7 mm. The combination of short range of the radioactive emanation and limited zone of sensitivity of the probe has permitted precise localization of the tumor and approximate determination of the boundary between gross tumor and relatively normal brain. The technique and results have been described (11, 12, 13). Upon exposure of the brain at craniotomy, probing counts are obtained first from an area presumed to be normal. The locus and depth of tumor are then determined by finding a spot with a much higher count rate, and the rough limits of tumor are ascertained by further appropriate probe counting.

Potassium, the principal intracellular cation, and hence the positively charged counterpart of the phosphate anion, has similarly proved to localize strikingly in brain tumors (14, 15). The highest ratio tumor:normal in the series of the former authors was 168:1; all of their meningiomas, glioblastomas and metastatic carcinomas yielded ratios greater than 20:1 if the biopsy samples were obtained less than six hours after the intravenous injection of isotope. Samples taken more than 18 hours after injection showed a much lower ratio, a respect in which potassium differs from phosphate, with which high differential ratios persist for days. K^{42}, the K isotope used, has a powerful 1.51 Mev gamma ray, as well as a beta radiation twice as energetic as that of P^{32}. However, Robinson's probe counter is inefficient for gamma radiation, and in practice, brain tumors have been located with it at operation about as effectively after K^{42} as after P^{32} injection.

False negative conclusions were reached: (*a*) when the probe did not enter

or graze the tumor, as in small deep metastatic nodules or tumors in thalamus or brain stem, (*b*) when a slow growing tumor took up too small an amount of isotope, and (*c*) in the presence of diffuse gliomatosis where no normal control area was available. Such false negatives were obtained in only five of 133 proven tumors. Conversely, high counts may occasionally be seen in normal brain several centimeters distant from tumor.

Confirmatory evidence of the value of the probe counting technique was presented by Morley & Jefferson (16); in 31 proven tumors they obtained false negative counts using P^{32} in only three slowly growing gliomas. Likewise, Garrity & Matthews (17) located 23 of 24 brain tumors with the probe counter and P^{32}; the patient they missed had bilateral, small, acoustic neuromas. These two groups of workers, and we as well, find that a probe counter survey of the bed of tissue removal for remnants of neoplasm has only rarely proved fruitful. Stapleton, McKissock & Farran (18) tried without success to construct a useful scintillation instead of Geiger-Mueller probe counter. In human cerebral samples they found P^{32} uptakes, tumor:normal, from 0.9:1 up to 34:1 in thirteen patients, and, like previous workers, found the lowest uptakes in sparsely cellular astrocytomas.

The probe counting technique, although simple, has not found widespread use, largely because the increasing accuracy of preoperative diagnosis leaves but few patients in whom the surgeon really needs the probing radioactive detector to find the abnormal tissue at operation. In this small minority, however, we have found the technique worth while. We have also found more recently that the differential concentrations of P^{32} are the greatest within a few minutes of the intravenous injection, at least in the glioblastomas subjected to continuous probe counting. It is consequently not imperative that this isotope be injected the day before operation, as we originally suggested. If the surgeon fails to find tumor in his initial steps after exposing the brain, he may usefully inject P^{32} and then count via the probe.

We had hoped additionally to be able to map out *en bloc* removals of gliomas with demarcation counts, remaining wholly within normal brain for the surgical incisions. No evidence has appeared to indicate that surgery of gliomas thus guided and performed gives better results. The count rates we have seen for uptake in different parts of histologically normal brain have at times overlapped those seen in brain slightly invaded by tumor. Hence our efforts at demarcation counting have been disappointing.

Diagnosis and localization of lesions before operation.—There appears to be a more fruitful manner in which to take advantage of the preferential uptake of many substances from the blood by focal intracranial lesions in contrast to normal brain. This consists in the use of radioactive agents emitting gamma rays which penetrate the skull, and whose focal origin may be detected by appropriate counters outside the intact head. Moore (19) was also the pioneer in this field, using his earlier observations with fluorescein as the clue to converting this to radioactive di-iodofluorescein. He and his colleagues (20) have shown that this substance also concentrates in tumors, up to 28 times

the levels in normal brain, and that many tumors may be spotted by extracranial measurements of radioactivity, especially with the more efficient scintillation counters now available.

Striking differences of opinion developed as to the likelihood of localizing tumors with this radioactive dye. On the one hand, Davis *et al.* (21) thought they "accurately diagnosed and localized" by this tracer test 92 per cent of 110 verified space-taking lesions. At the other end of the scale, Belcher, Evans & de Winter (22) localized only one of 20 verified brain tumors, although they made an intensive effort to achieve a maximally precise technique. Subsequently, Davis & Goldstein (23) withdrew the claim of such remarkable precision for the method, classifying as inaccurate 64 of their 200 tests on patients in whom the diagnosis was verified at operation or autopsy. The original proponents of the method reported 22 tumors correctly localized, whereas 20 tumors proven to be present were not located (9). Seaman, Ter-Pogossian & Schwartz (24) are in agreement with this, having a score of 46 per cent correct radioactive foci in 65 patients with histologically verified tumors. Svien & Johnson (25), however, found localization "precise enough to be of use to the surgeon" in only about 20 per cent of patients with brain tumors. Sjögren (26), after experience with the method in 30 cases, was also discouraged; he said "pneumography and/or angiography are . . . always to be preferred." Schlesinger (27) used the method for a time, and Nechaj & Moses (28) have described the scintillation counting equipment they employ for the test. Tabern of the Abbott Laboratories succeeded promptly in eliminating the disadvantages of I^{131} splitting off from the dye and entering the thyroid gland. He prepared the labeled compound in pure stable form. But the dye is excreted so rapidly into the faeces via bile and into the urine that the counting rate diminishes briskly over all parts of the head. Within three hours both a useful count rate and the differential concentration between tumor and normal have largely disappeared. Initially, the survey of the head required as much as four hours; however, with the change to scintillation counters having circa 40 times the efficiency of bismuth-coated Geiger counters, lower doses of about 0.25 mc. and 30 to 40 minute times for the survey sufficed. Langer & Loevinger (29) developed a logical tactic for acquiring and plotting the data in view of these changes occurring during the study.

But an even more useful step forward was taken by the Minnesota group when they found that radioactive iodinated human serum albumin (RIHSA) will also concentrate more in intracranial lesions than in normal brain (30). This compound is excreted in the urine much more slowly; only 15 to 20 per cent passes out in the first day. It has proved fruitful to make serial counts on each of two or three days, because at times the differential uptake increases in a later study. In a subsequent report by this same group, 71 per cent of 17 tumors were localized by scintillation counting of RIHSA (31). Dunbar & Ray (32), using RIHSA with similar equipment, localized 61 per cent of 41 proven intracranial tumors. Ashkenazy & Crawley (33) agreed that the RIHSA gives better results, and Farmer *et al.* (34) have also taken up the

method. Yuhl, Stirrett & Libby (35) have found too that studies with RIHSA are more accurate than those with the iodinated dye. Baudouin & Planiol-Dupeyron (36) agreed after studying 12 tumors that the localization seemed more definite on the day following injection than on the same day; even so, four tumors of the cerebral hemispheres were missed. The Mayo Clinic group localized only 30 per cent of the 36 intracranial tumors they studied with this newer agent and have concluded that it is "not, in its present stage of development, a useful method for localization of intracranial lesions" (37).

NaI^{131} has also been tried by Chou, Moore & Marvin (38), but early hopeful results with it were not sustained by their later experience. Farris, Correa & Pantek (39), after using this agent for over two years, obtained an accuracy of 60 per cent in their 50 microscopically verified tumors. In their semiautomatic technique a pair of scintillation counters is moved together, one on each side of the head. The count rates from the two sides are balanced against each other so that, when equal, a recording pen traces a line down the center of a chart. A relative increase of the count rate on one side causes the recorded line to deviate to that side.

Another gamma emitting radioisotope which has had a trial is K^{42}. Selverstone, Sweet & Ireton (14) found definite localization of activity in eight of 10 supratentorial tumors and in none of five that were infratentorial. Susen, Small & Moore (15) spotted six of 10 supratentorial and one of nine infratentorial tumors. Both of these groups found the enormous uptake of the K^{42} by temporal and posterior cervical muscles and the short (12.4-hr.) half-life militated against its practical use. Kramer, Burton & Trott (40) have acquired a large experience with this isotope over the past several years, however, and report that 56 per cent of 82 proven brain tumors were localized with their current instrumentation. Sweet & Brownell (41) have been impressed by the high neoplastic uptake of K^{42}, and use it in special cases with few symptoms if an arsenic scan is normal.

A disadvantage of the use of gamma rays to localize a concentrated source of radioactivity is the scatter of these rays as they traverse matter. At the surface of the head, then, there ensues a blurred, enlarged image of the intracranial lesion. The existence of a special kind of paired gamma rays arising at the "annihilation reaction" makes possible, however, the rejection by appropriate counting equipment of the scattered gamma rays. When a positron is given off at radioactive decay, it collides with an electron within a fraction of a second; the two particles are "annihilated" as mass, and appear as the energy of two gamma rays which leave the scene back to back—i.e. at a 180 degree angle. Electrical circuits associated with a pair of scintillation counters on either side of the head can be so arranged that no count is recorded unless each member of the gamma ray pair strikes its detector. If one ray is scattered, no count occurs—a so-called coincidence counting system. The concept of using a positron-emitting isotope was evolved independently at Harvard and Duke universities [Sweet (42); Wrenn, Good & Handler (43)]. The latter investigators attempted to use it with the short half-lived Cu^{64} synthe-

sized into the dye copper phthalocyanine. After a preliminary report, they gave up further work.

Brownell & Sweet (44), however, have found that the more practical positron-emitter, As^{74} (17-day half-life), concentrates well in intracranial lesions in the simple form of arsenate or arsenite ions, precluding the need for chemical synthesis. For the test, the requisite 20 μc. per kg. of body weight requires a maximal dose of only 0.2 mg. of metallic arsenic to a 100 kg. person; a common daily dose of potassium arsenite (Fowler's solution) contains 7 mg. of arsenic, so chemical toxicity is no problem. The positron-emitters As^{72} and As^{74} are produced in the cyclotron, and are hence more expensive than reactor-produced isotopes.

Brownell, in addition to conceiving the idea of using positron-emitters, has also built an automatic scanning apparatus which presents the data as a life-size picture. During a continuous scan of the whole side of the head, stamp marks are made on paper to indicate the concentration of coincidence counts. The area of tumor stands out in the lateral view as a zone of increased density of such counts. This picture, called a positrocephalogram or PCG, gives no clue, though, as to the lateralization of the lesion. Such information is provided by another type of scan which emerges simultaneously as a record of the asymmetry of the total gamma radiation (not just the coincidence counts). The nearer the area of increased isotopic uptake to one of the two detectors, the greater the total gamma count there because of the inverse square effect of increasing distance. A curved stamp mark for right-sided increased uptake and a straight line for left-sided increase have been used arbitrarily to lateralize the lesion, yielding what we have called an asymmetrogammagram, or AGG. In addition to the check on a questionably abnormal zone provided by each type of scan, readings on successive days serve the same purpose. Uptake in muscle is often much less pronounced on the day after injection, permitting basal tumors to be seen more clearly. Numerous illustrations of the type of picture obtained in the PCG and AGG are given by Sweet & Brownell (41). At their latest report, Brownell & Sweet (46) had located the tumor in 69 per cent of 207 patients with proven neoplasms.

It became apparent early in the intracranial localization studies that tumors were detectable not so much because they took up extraordinarily large amounts of radioisotopes but because the normal brain took up so little. The long known formidable character of the "barrier" between blood and normal brain is, then, the basis for the utility of the method in intracranial tumors. In a few other sites in the body, e.g. eye and breast, neoplasms grow in tissues giving a very low background of isotopic uptake, and the method can likewise be used.

The workers in the field are in general agreement that the sparsely cellular, most slowly growing gliomas and the congenital intracranial tumors tend to take up only small amounts of isotope and are often missed. The tiny amount of neoplastic tissue in many tumors of the brain stem, of the midline ventricles, and of the sellar region also leads to many misses in these areas; they are, however, usually well diagnosed by other means. Cystic fluid takes

up even less isotope than normal brain, and the low concentration in the fluid may counterbalance the larger amount in the tumor nodule. Great cellularity appears to be an important feature in determining high isotopic uptake, which occurs both in meningiomas, even the slowly growing calcified ones, and the malignant glioblastomas and metastatic tumors. Tumors occupying the cerebral hemispheres are the ones most likely to be diagnosed isotopically, a fortunate circumstance since in this locus a combination of arteriography and pneumography is most likely to fail. Yet it is just these tumors which one wishes to spot early—in the case of gliomas, while extensive cerebral resection will leave a useful person who will perhaps be a good candidate for boron—slow neutron capture therapy (45), and, in the case of meningiomas, while total resection will carry a minimal morbidity and mortality. Tumors near the surface of the cerebral hemispheres are especially likely to be detected by isotopic methods. It is in just this type, in which a few convulsions often occur at an early stage, that prompt diagnosis has been out of reach.

Brownell & Sweet (46) have shown in PCG and AGG and then successfully removed in three patients a small tumor of a cerebral hemisphere missed by both air study and arterial injection in each instance. Two of these were meningiomas, the tumor type yielding their best diagnostic results—33 out of 34 correct. Benda, David & Constans (47) have also found a high uptake of arsenic ion by meningiomas.

Ashkenazy & Crawley (33) have emphasized the value of their tests with RIHSA in the early detection of neoplastic recurrences—an important field of usefulness because of the notorious difficulty in interpretation of postoperative pneumograms and angiograms. Brownell & Sweet (46) point out that it is necessary to have serial scans for this purpose—one a month or so postoperatively after the blood-brain barrier has fully recovered from the original operation; these serve as a base line for interpretation of subsequent scans. Serial isotopic studies as often as indicated are harmless to the patient, a feature which is also valuable in the critically ill, who may tolerate poorly intraventricular or intraarterial injections.

The blood-brain barrier is disturbed, however, by a variety of lesions other than tumors. Among these, a consistent and substantial increased uptake occurs with abscesses. Brownell & Sweet (46) found focal abnormality in the scans of seven of their nine patients in this category. Seaman *et al.* (24) localized one chronic abscess and missed another in the acute stage, using the radio-dye. Davis *et al.* (21), with the same agent, apparently located the two abscesses they studied. Farris, Correa & Pantek (39) also mention that with a positive radioisotopic survey "one may be reasonably sure that tumor or abscess is present."

In some vascular lesions there is also a breakdown of the blood-brain barrier with increased isotopic uptake. The ischemic area of brain after a thrombosis may give rise to an abnormal isotopic focus as seen in one patient of Peyton *et al.* (31), but in none of three patients of Dunbar & Ray (32)—all four were studied with RIHSA. Of 38 patients of Brownell & Sweet (46) with

cerebral thrombosis or hemorrhage the As^{74} positron scans were abnormal in nine, but unequivocally so in only two. In each of these, the ictus was recent and later scans returned toward normal. This behavior gives the method value in distinguishing between purely vascular lesions and those tumors, with such an abrupt onset of symptoms followed by some recovery, which simulate a cerebral vascular accident. In the patient with neoplasm, the original scan is usually more clearly abnormal, and it improves little or none on repetition.

In chronic subdural hematoma, Peyton *et al.* (31) recorded an abnormal focus in one patient, and Dunbar & Ray (32), strikingly diffuse unilateral abnormality in four patients. The latter did not find an increased amount of RIHSA in the hematoma fluid; they presume the increase was in the underlying brain. Brownell & Sweet (44) found three positive As^{74} scans in instances of unilateral subdural hematoma, and a negative scan in a patient with bilateral symmetrical hematomas.

Substantial improvements in both instrumentation and differential isotopic uptake may well be achieved. However, the current method has, I think, practical clinical value because its harmless, painless character permits its serial use when the index of suspicion of intracranial mass is low. Moreover, in the critically ill, as well as other patients, sufficiently precise localization has been obtained to give the neurosurgeon adequate information without resort to angiography or pneumography, each of which carries some risk.

Formation and Absorption of Cerebrospinal Fluid

Prior to the advent of isotopic tracers, the cerebrospinal fluid (CSF) was generally thought to arise in the cerebral ventricles from the choroidal plexuses [Dandy (48)], and to flow thence through the openings of Magendie and Luschka into the subarachnoid spaces. Here absorption was presumed to occur—mainly at the arachnoidal villi in the view of Weed (49), mainly at the blood vessels of this space according to Dandy (50). Implicit in virtually all work in the pre-isotopic era (including that in disagreement with the above concepts) was the assumption that the CSF arose in toto at one or more sites, flowed elsewhere to other places where all constituents were absorbed. Almost any traceable dye or other chemical studied was considered to be representative of the entire CSF. However the need for better methods of study was recognized by many in the field, including two of the major contributors, Weed (51) and Flexner (52). The latter, in a superb critique of the major work on this fluid, pointed out that many of the "most elementary problems still receive dissenting answers and agreement today often exists only within the school of a particular investigator." Some headway at resolving the discrepant experimental results and conclusions has been possible now that the normal components of the CSF can be studied with their isotopic counterparts. Such studies have indicated that the molecules of all the substances studied are moving in opposite directions simultaneously back and forth across all membranes and sheets of cells throughout the CSF path-

ways—as would be expected by the behavior of the body constituents elsewhere. The processes of formation and absorption[3] studied with isotopes prove to be taking place ubiquitously, and, moreover, they are taking place at rates which vary strikingly from one normal constituent to the next. Hence the problem has become, if anything, more formidable, and requires the quantitative determination of net rates of transfer in one direction compared to the other at each site for each component of the fluid for a fuller understanding of all the mechanisms involved. The studies to date have perhaps done more to reveal the full scope of the problems than to give definitive answers to outstanding questions. A review of the basic earlier work, as well as of more recent isotopic studies is being presented by Sweet *et al.* (53). Here I am summarizing only the studies of the last seven years.

Formation of CSF

The ventricles.—The rate of entry of Na^{24} into lateral ventricle, cisterna magna, and lumbar subarachnoid space was measured following intravenous injection of Na^{24} chloride by Sweet, Solomon & Selverstone (54). They and Sweet & Bakay (55) studied patients with presumed normal CSF systems as well as others with "pseudotumor cerebri," the syndrome of idiopathic increased intracranial pressure with papilledema and normal sized ventricles. Tiny samples were counted to minimize upset to the CSF dynamics. They used the time required for attainment at a CSF site of one-half the isotopic concentration in the plasma at two hours as an indicator of the rate of entry of Na^{24} from plasma ($t\frac{1}{2}$). The rise in concentration of ventricular Na^{24} was always much faster than that in the cistern which in turn always exceeded somewhat that in the lumbar region. Thus in one normal man, $t\frac{1}{2}$ for the ventricles was 15 min., for the cistern 5 hr. and 22 min., and for the lumbar region 9 hr. and 4 min. In 11 such studies on nine patients with pseudotumor cerebri, the curves had the same general relation to each other. The Parisian workers (56, 57) made similar studies with a similar method. They expressed their results at the CSF sites in terms of percentage of the plasma level taken as 100 per cent one hour after injection. In fifteen normal adults they found ventricular levels at 35–60 per cent and lumbar levels at 2–18 per cent with an average of 6 per cent. The cisternal figure was 12 per cent. In 12 normal children they found a faster rate of exchange at the lumbar region than in the adults; the average was 15 per cent, with a lower figure for those children above seven years of age. When we express our results in the same way, our lone presumed normal adult had the following figures relative to the plasma at one hour: ventricular 73 per cent, cisternal 17 per cent, lumbar 3.8 per

[3] Whenever a particle enters the CSF, we have spoken of the process as contributing to the formation of the fluid; whenever a particle leaves the CSF, we have used the term "absorption" to describe the movement. Others may prefer to use the term "formation" to refer to the net transfer or net entry into the CSF at any given locus; correspondingly, "absorption" would then refer to the net removal or net departure from the CSF at any site. To signify such changes, we have added the adjective "net" to terms denoting income or outgo.

cent. In ten studies on patients with pseudotumor the range was: for the ventricles 61–87 per cent, averaging 76 per cent; for the cistern 14–38 per cent, averaging 20 per cent, and for the lumbar region 3.0–21 per cent, averaging 7.9 per cent. Three of the ten studies were in children. A change in the technique in two more of our normal adults involved the intravenous injection of nearly 200 cc. of heavy water along with the Na^{24} in each of them. This yielded one hour figures as follows: ventricular 32 per cent and 31 per cent, cisternal 11 per cent and 10.6 per cent, and lumbar 5.5 per cent and 3.7 per cent. Much less rapid mixing and a lower Na^{24} content of many of the early plasma samples were probably responsible for the slower rate of appearance in the ventricles in these two patients.

The slowness of the rate of exchange of sodium between plasma and all parts of the CSF including the ventricles can be appreciated by comparison with the figures for exchange with the general extracellular fluid. Flexner, Cowie & Vosburgh (58) found that 78 per cent of the plasma sodium in man is exchanged each minute with intravascular sodium. Bakay, Selverstone & Sweet (59) measured rates varying from 66 to 150 per cent per min., although the latter high figure was obtained in a subject who was vigorously active during the period of sampling. In the CSF the maintenance for many hours of markedly different isotopic concentrations in various portions of the fluid is evidence of exceedingly sluggish mixing and flow. By contrast again with the blood, a small amount of Na^{24} chloride injected into a vein in the human arm is completely mixed in the veins and arteries from the groin upward within 3 min. (59).

The subarachnoid space.—The foregoing data from Na^{24} are all consistent with the concept that the CSF enters largely or entirely in the ventricles, flowing out of them for absorption. An abundance of evidence has, however, accumulated to indicate that substances enter the lumbar fluid below a complete spinal block. In the pre-isotopic era, Cestan, Laborde & Riser (60) and Wallace & Brodie (61) demonstrated in dogs with complete thoracic blocks produced by ligatures that substances injected intravenously appeared in the lumbar region. The normal constituent urea was used in large amounts by the first authors, as well as sodium salicylate in other studies; the second group used bromide.

Tubiana, Benda and Constans (56) were the first to study a patient with a complete spinal block. To a person with a cervical lesion they gave Na^{24} chloride intravenously and obtained a concentration in the lumbar CSF at one hour which was 15 per cent of that in the blood, or well within the range of their normals. Sweet and Benda repeated this study in another patient with a post-traumatic mid-thoracic block which was maintained long after injury and laminectomy because the sixth thoracic vertebra was displaced to lie almost directly in front of the seventh vertebra. We thought him an especially favorable subject for analysis of the behavior above and below the block more than one month after injury, because we should expect minimal if any pathologic processes in the walls lining the open portions of the subarachnoid space at that time. Here, too, the Na^{24} entered the lumbar sac

rapidly. In fact, the rate of entry here was almost as fast as into the cistern [see Sweet *et al.*, Figure XI (53)]. Boldrey *et al.* (62) have also found, in a patient whose CSF was divided into two completely separate compartments by an epidermoid tumor of the third ventricle, that both $Na^{24}Cl$, and P^{32} injected intravenously as the phosphate, entered the lumbar sac about as rapidly as they did the lateral ventricle. The high total protein of 210 mg. per cent in the lumbar fluid and 266 mg. per cent in that from the ventricles suggested that there was abnormal permeability of vessels about the tumor both above and below the block. Hence the exchanges observed with rapid entry here were probably not characteristic of the normal. In fact, the Parisian workers, Tubiana *et al.* (56) and Benda *et al.* (57), in studies in over 125 patients with tuberculous meningitis, have found a strikingly abnormal rapid rate of entry of Na^{24} into the lumbar sac. The concentration was greater than 20 per cent of the plasma level in one hour in 80 per cent of these patients, averaging 35 per cent. That this was due to an abnormal permeability in the spinal canal, and not to more rapid flow from the ventricles, was shown by the unusually low concentrations at that site in this disorder, averaging 15 per cent at one hour, or about one-third the normal.

Further evidence, however, that the normal membranes lining the spinal canal pass normal constituents directly into CSF was provided by Eichler, Linder and Schmeiser (63) in dogs. After exposing five sites of the spinal dura between sacrum and cistern, they injected Na^{24} intravenously. The concentration of Na^{24} twenty minutes later was highest in the lumbar area, intermediate in the thoracic region and lowest at the cistern. Although this reverses the cisternal:lumbar ratios seen in man, it does indicate that the dog is passing Na^{24} directly into the lumbar area. The work of Crow (64) in dogs included studies which showed that, after extradural thoracic ligature, Na^{24} entered the lumbar region directly from the blood.

The first demonstration of extraventricular origin of a component of the CSF in man under normal dynamic conditions of the body fluids came as a surprise when D_2O and $Na^{24}Cl$ were injected together intravenously. In fact, this study also demonstrated that the water of the CSF was leaving as well as entering the fluid throughout its compartments. Sweet, Selverstone, Soloway & Stetten (65) carried out this study in two middle-aged men. The rate of entry of the Na^{24} in them at the three CSF sites sampled has already been described. Study of the simultaneous behaviour of D_2O showed a vastly greater velocity of entry of the water molecules at all three points, and an unexpected increased rate of entry at cistern as compared with ventricle. The comparative rates are given in Table I. One sees that D_2O enters the cisterna magna five to eight times as fast as it does the ventricle. In contrast, entry of the cisternal Na^{24} is at less than one-fifth the rate of that of the ventricular Na^{24}. Since the total sodium ion is at the same concentration throughout the CSF, the isotopic tracer behavior is explicable only on the basis of movement of water both into and out of the CSF across the barrier between it and blood at all the sites studied. The water in the blood moves toward equilibrium with that in the ventricle eight or ten times faster than sodium at this site, and the

TABLE I

TIME REQUIRED FOR ATTAINMENT OF ONE-HALF ISOTOPIC CONCENTRATION AT EQUILIBRIUM

		Na^{24}	D_2O
Patient H.D.	Ventricular	83 min.	8.1 min.
	Cisternal	370 min.	1.5 min.
	Lumbar	600 min.	18.6 min.
Patient E.C.	Ventricular	82 min.	11.0 min.
	Cisternal	370 min.	1.4 min.
	Lumbar	550 min.	25.5 min.

movement toward equilibrium at the cistern is roughly 250 times as fast for water as for sodium. Since, therefore, much water unaccompanied by electrolyte is entering these areas from the blood, a corresponding quantity of water must be moving at the same time in the opposite direction; otherwise the fluids would become progressively more dilute. Moreover, since the movement of water into the cistern is so much faster than that into the lateral ventricle, the former must be largely independent of choroid plexus or ependyma. The ratio of transfer rates sodium to water was determined at each site by dividing the Na^{24} counts per 0.1 cc. per min. by the atom per cent excess D 40 min. after injection, yielding an average for the two patients of 462 for the ventricle, 154 for the cistern and 80 for the lumbar region. From this we saw that the more rapid entry of water than sodium was most pronounced in the lumbar region and least in the ventricle. The greater complexity and thickness of the ependyma and choroid plexus than that of the pia makes the faster exchange of water in the subarachnoid space less surprising after all.

The speed of movement of the water molecules is so great that it is difficult by isotopic methods to determine the direction of their net transfer. Thus, with a $t\frac{1}{2}$ to equilibrium in the normal ventricles at about 10 min., the per cent of ventricular water exchanged per minute equals $0.693 \times 100/10$, or 7 per cent per minute. With ventricles of 30 cc. volume, we then have an exchange of 2 cc. per min., or about 3 l. per day. But our measurements of accumulation of fluid at constant pressure in the normal ventricles average less than 100 cc. per day, or only about 3 per cent of the amount exchanged. Consequently, the limits of accuracy of present isotopic methods make it difficult to measure by comparison of rate of entry and leaving the net accumulation of water.

Bering (66) confirmed the rapid movement of D_2O from blood to various sites in the CSF in normal man and also in the dog. He found the $t\frac{1}{2}$ to equilibrium much shorter in the three infants than in the two adults he studied. He also measured the rate of appearance of D_2O in the lumbar region in two patients with lesions which divided the CSF into two compartments. In a 14-month-old infant with a block at the aqueduct of Sylvius, the $t\frac{1}{2}$ at 20

min. seemed to fall within the range of normal suggested by his figures of 18 and 7 min. obtained from two normal infants aged respectively six and eight months. Likewise, a 14-year-old patient with a block at the foramen magnum had a $t\frac{1}{2}$ of 33 min., again within the range of his two normal adults, who showed lumbar subarachnoid half-times for D_2O appearance of 32 and 38 min. From rough measurements he made, Bering concluded that the rate of appearance of D_2O at any site in the CSF was proportional to the ratio of surface area to volume of the compartment in question. The relative importance of this factor to the one we mentioned of complexity of tissue lining the compartment has not been determined.

Inasmuch as comparisons between ventricular and subarachnoid behavior are most readily made by the study of patients with blocks between the two areas, Sweet and Locksley (67) selected two patients with small, virtually static lesions blocking outflow from the posterior part of the third ventricle for many years previous to the study. Torkildsen's operation of placing a bypassing catheter between one lateral ventricle and the cisterna magna had been carried out over five years before; following this operation, each had maintained essentially normal intracranial pressure, although at the time of study the first three ventricles of each were grossly dilated at 623 cc. and 440 cc. respectively. By occlusion of the Torkildsen catheter during the period of study, the CSF was separated into two compartments, one consisting of the first three ventricles, the other of the fourth ventricle and subarachnoid space. Into each patient a simultaneous intravenous injection was made of Cl^{38} and K^{42}, representing respectively major extracellular and intracellular ions. The curve of rise in concentration of Cl^{38} in the largely subarachnoid compartment, sampled via a lumbar needle, was essentially the same as that for each lateral ventricle, demonstrating that Cl^{38} was entering the normal subarachnoid space directly. Since the volume of the purely ventricular segment was about eight times that of the largely subarachnoid sector, Cl^{38} was entering the ventricles roughly eight times as fast as it was entering the subarachnoid space. The figures for K^{42} revealed a much more rapid rise in concentration at the lumbar needle than in the purely ventricular compartment; the correction for volume showed that K^{42} was entering a unit amount of purely ventricular fluid a little faster than it was entering directly such amount of subarachnoid fluid.

The special importance of the ventricles in supplying the extracellular ions to the CSF has been neatly shown by Crow (64). He measured the concentration of Na^{24} in the brain stem after intravenous injection when the flow of CSF was normal, and when most of the ventricular flow was directed away from the brain stem by a catheter in the aqueduct of Sylvius. In the latter situation, the brain stem contained only about half as much Na^{24} as it did when the flow was normal.

In the greatly dilated lateral and third ventricles in the patients of Sweet and Locksley (67), the choroid plexus and ependyma may not have behaved normally. Sweet *et al.* (53) studied two other patients with tumors in the posterior part of the third ventricle, in each of whom the ventricular system

had returned to normal size following the ventriculo-cisternostomy operation. In one of these, Na^{24} and Cl^{38} were injected intravenously after the bypass catheter was clamped. The curves for each of these two isotopes rose in the cisterna magna at a rate roughly similar to that in the normal lateral ventricle. Inasmuch as the choroid plexus in the fourth ventricle weighs only about one-fourth or less that in the lateral ventricle, the isotope emerging from the fourth ventricle into the cisterna magna was probably insufficient to account for all of that found in the cistern. It seemed clear that in this more normal situation, the two major extracellular ions enter the subarachnoid space as well as the ventricles directly.

There is also evidence that substances enter the cerebral subarachnoid space directly. Wallace & Brodie (61) found, in dogs, intravenously injected iodide in higher concentration in this space than in the cisternal fluid, with even greater concentration in the cerebral cortex adjoining the space. They concluded "that substances pass from the blood into the CSF not only by way of the choroid plexuses but also directly by way of the extracellular fluid." Sweet *et al.* (53) used P. Benda's suggestion for collecting blood-free subarachnoid samples of CSF via lens or filter paper to study a patient with a normal central nervous sytem. Intravenously injected Na^{24} chloride was found in similar concentrations in cisternal and cerebral subarachnoidal samples, demonstrating that most of this ion in the space over the cerebrum enters directly.

Entry of protein into CSF.—Wasserman & Mayerson (68) found no radioactivity in the CSF after injecting intravenously either canine or human albumin labeled with I^{131}. Fishman (69), however, found RIHSA in the cisternal fluid of dogs in less than 40 min. after an intravenous injection. Equilibrium between this site and the plasma was reached in about 20 hr.; the biological half-life of the RIHSA averaged 6.3 days in plasma and 8.0 days in cisternal CSF. Studying the patient with mid-thoracic traumatic block mentioned previously, Sweet *et al.* (53) found, after intravenous RIHSA, that the labeled albumin entered directly the lumbar spinal compartment as well as the cisternal area. The total protein in the lumbar CSF was 1000 mg. per cent; that in the cistern was 16 mg. per cent, but the labeled protein entered the cistern faster than it did the lumbar area, demonstrating that in this instance defective absorption alone, without abnormally rapid entry of protein into the lumbar CSF, was responsible for the high lumbar protein concentration. Fishman and Ransohoff (70) have reported studies on hydrocephalic infants in which they found specific activities of RIHSA in the CSF to increase in the order of ventricle to cistern to lumbar regions in measurements 6 to 9 hr. after intravenous injection.

Conclusion.—From the isotopic studies, there is agreement that water enters a unit volume of subarachnoid space about as fast as, or at some points even faster than, it enters a similar volume of the ventricles. Flow from the ventricles accounts for a tiny fraction of the water molecules entering the subarachnoid space. The major monovalent normal electrolytes enter the subarachnoid space directly. Sodium and chloride move at similar speeds and

enter a volume of ventricular fluid much more rapidly than they do the same volume of lumbar fluid. Protein also enters the subarachnoid space directly.

Absorption of CSF

Although there has long been general acceptance that absorption of the CSF takes place in the subarachnoid space, the question of absorption from the ventricles has been controversial. Russell (71) summarized the earlier pertinent studies and stated that these data "may reasonably be regarded as evidence of absorptive activity but by no means preclude concomitant secretory activity. For this the renal epithelium provides a physiological parallel." The isotopic studies have borne her out.

D_2O.—We have already seen that D_2O is absorbed rapidly and directly from the ventricles. Sweet and Locksley (67), on a patient with a clamped Torkildsen tube, found, after injection of D_2O into the CSF, a disappearance half-time in enormous ventricles of 40 min. Bering (72), in two infants also with obstructive hydrocephalus, found "ventricular exchange half-times" of 100 min. and 180 min. respectively. Sweet *et al.* (53), in their patients with much smaller (normal) sized ventricles studied during clamping of a Torkildsen catheter, found the expected shorter disappearance half-times, usually varying between 22 and 30 min. Similar disappearance rates were usually found at cisternal and lumbar samples as well. Even in one patient with a significant flow out of the ventricles into the cistern as measured by RIHSA, the D_2O exchanged so fast through the ventricular wall that the accuracy of the method did not permit determination of the relatively small amount of heavy water flowing through the aqueduct. Bering (72) also measured the same rate of appearance of D_2O in sagittal sinus blood in an infant before and after arachnoido-ureterostomy for communicating hydrocephalus—this despite the fact that the shunt was eliminating about 150 cc. of CSF daily via the bladder.

Electrolytes.—Sweet & Locksley (67) and Sweet *et al.* (53) also injected K^{42}, Na^{24}, and Cl^{38} into the two separate CSF compartments of their patients with closed Torkildsen tubes and found that these ions all leave a closed purely ventricular compartment. In two patients with enormous ventricles, the disappearance half-times were 4.3 and 8.2 hr. for K^{42} and Cl^{38} respectively from a ventricular volume of 440 cc., and 4.1 and 8.9 hr. for K^{42} and Cl^{38} respectively from a ventricular volume of 621 cc. The Na^{24} and Cl^{38} curves showed these ions leaving the normal-sized purely ventricular compartment at roughly similar rates to those from the largely subarachnoid section of the CSF spaces. In numerous simultaneous studies, Na^{24} and Cl^{38} were absorbed at rates almost identical to each other at any particular site.

Protein.—A striking dissimilarity was usually found between the ventricular compartment and the largely subarachnoid compartment with respect to the rate of absorption of RIHSA instilled into each. A slower rate of leaving the closed ventricles applied both in patients in whom these cavities were huge and in whom they were normal in size. Thus, in a girl in the latter group with normal intracranial pressure, the concentration in the subarach-

noid compartment (corrected for mixing) dropped to one-eighth the original level in about 5 hr., at which time it was over one-half the starting level in the ventricles [Sweet & Locksley (67); Sweet *et al.* (53)]. On the basis of these findings, one might hypothecate that the arachnoidal villi have the special task of absorbing CSF protein. These structures would then have a function relative to CSF analogous to that of the lymphatics and the general extracellular fluid.

That an impaired rate of absorption of protein from the subarachnoid space may be a sign of impending increased intracranial pressure was suggested by the course in one of the patients studied on three occasions by Sweet *et al.* (53). And, in fact, at a later stage, increased intracranial pressure may be caused by an elevated protein content of the CSF. Gardner, Spitler & Whitten (73), as well as Love, Wagener & Woltman (74), have described patients with tiny nonobstructive intracranial tumors, or tumors in the spinal canal, in whom a high CSF protein and increased intracranial pressure with papilledema returned to normal upon removal of the tumor. Gardner *et al.*, Drew & Magee (75), and Denny-Brown (76) have also reported increased intracranial pressure and papilledema along with the high protein of the syndrome of Guillain-Barré. Most of these authors attributed the increased pressure to mechanical clogging by the protein molecules of absorbing mechanisms, rather than ascribing a significant role to the slightly increased osmotic tension in the CSF.

Role of the Choroid Plexuses

Bourdillon *et al.* (77) have combined NaBr and $Na^{24}Cl$ for intravenous injections in man. They confirm the previously mentioned findings for the behavior of sodium; they find, however, that the bromide enters the normal lumbar CSF much more rapidly than it does the ventricle. The same sort of behavior with respect to uranium salts has been seen by Sweet, Luessenhop & Gallimore (78). They gave this heavy metal either as the hexavalent or tetravalent ion intravenously, and in six of seven patients found that the lumbar samples contained larger concentrations of the uranium than did the ventricular samples. We see here, then, a selective retardation by the choroid plexus and ependyma of the anion bromide and the cations of tetravalent and hexavalent uranium, as well as a more rapid transfer of these ions directly into the subarachnoid space.

Bering (79) has studied the rate of exchange of D_2O between blood and ventricular CSF in an infant with obstructive hydrocephalus before and after bilateral choroid plexectomy. He has also measured the same rates for D_2O, Na^{24}, K^{42} and RIHSA in hydrocephalic dogs before and after choroid plexectomy. The operation "did not seem to affect these exchanges, except possibly the early fast phase of K^{42} exchange." The net rates of transfer of water were perhaps too small to be detected by the accuracy of his methods.

Certainly a vast body of clinical evidence has piled up to indicate a dangerous capacity of the choroid plexuses to pour CSF into the ventricles despite obstructions to flow and absorption. Prevention of outflow from even

so small a part as the temporal horn of one lateral ventricle may be lethal [Cairns *et al.* (80)]. In two of their patients, the removal of only that part of the choroid plexus in the isolated temporal horn restored the intracranial pressure to normal—excellent evidence of the power of the choroid plexus to produce CSF despite a high pressure in the cavity containing it. Another proof of excessive formation of CSF by cells of the choroid plexus was provided by Kahn and Luros (81) in a patient with a papilloma of one choroid plexus. The patient's papilledema, increased intracranial pressure, and grossly dilated ventricles were all restored to normal by removal of the tumor. Ray (82) also had experience demonstrating the extraordinary capacity of the cells of the choroid plexus to form CSF. In a 4-month-old infant with a CSF normal in composition and grossly dilated ventricles, he treated the communicating hydrocephalus by arachnoido-ureterostomy. So much fluid was passed with the urine that adequate fluid intake was not being maintained even by parenteral administration. Hence the catheter was transferred from the ureter to the peritoneal cavity, whereupon gross abdominal distention developed which embarrassed mobility and respiration. A papilloma of the choroid plexus of each lateral ventricle was then demonstrated as the cause.

CSF—Secretion or Ultrafiltrate?

The selective capacity of the ventricles to pour out sodium and chloride, but to hold back bromide and uranium, together with the relentless capacity of the choroid plexuses to accumulate CSF to the extent of destroying the brain, argue strongly that this portion of the CSF is secreted. Other isotopic evidence in favor of that theory was provided by Greenberg *et al.* (83). In dogs injected intravenously with radioactive K, Na, Br, Rb, Sr, PO_4 or I, the rate of increase in concentration in cisternal CSF of the labeled ions varied greatly. The rate of entry decreased in the order the foregoing ions were named. The grossly variable, marked hindrance to the free passage of ions into the CSF is further evidence that a process of secretion is involved.

The abundant evidence of extraventricular entry of constituents of the CSF has also been cited. This occurs without the power presumably provided by the choroid plexuses. Nor does there seem to be any structure lining the subarachnoid space which would be a likely performer of such work. Consequently, Sweet *et al.* (53) have concluded that the portions of CSF which enter it via the cerebral perivascular spaces, the linings of the subarachnoid space, the vessels in that space and perhaps the ependyma are passing in (and out) at rates determined by the permeability of the cell or membrane and the balance of hydrostatic and osmotic pressures at that point—i.e. by a process of ultrafiltration or diffusion. It would seem that the proponents of the two concepts of CSF formation are each partially right, that the choroid plexus cells are secreting fluid, but that ultrafiltration is occurring in most of the rest of the wall of the CSF spaces. The data are not yet at hand to test mathematically the validity of this concept. An indication of the vast amount of work yet to be done on this score may be gained by perusal of papers on

the aqueous humor, whose students are far ahead of us [Kinsey & Palm (84); Davson (85)]. A particularly intriguing new tool is the agent, acetazoleamide (Diamox). Tschirgi, Frost & Taylor (86) have shown that this potent inhibitor of the enzyme carbonic anhydrase causes in cats and rabbits a marked decrease in the rate of CSF formation and a marked reduction in intracranial pressure. The hypothesis proposed by these authors is that the formation within the blood-brain barrier of H^+ and HCO_3^- is a prerequisite for the entry into both the interstitial fluid of the brain and the CSF of plasma anions and cations, that the Na^+ and Cl^- leave the blood by exchanging in the blood-brain barrier with H^+ and HCO_3^-. Such possibilities make it even more mandatory that investigators in this field familiarize themselves with the newer knowledge of the whole field of membrane permeability. The book of Davson and Danielli (87) is an excellent starting point for this.

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AUDIOLOGY[1]

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Introduction

Since this is the first article on the subject of audiology to appear in the *Review* and many of its readers may find audiology a new word, and certainly some will find nomenclature new and confusing, a few definitions and explanations seem in order. It also seems appropriate to discuss some accepted principles. Audiology, the science of hearing, has many branches and many kinds of specialists calling themselves audiologists. For example, otologists specializing in hearing conservation and rehabilitation, clinical audiologists, nonmedical specialists concerned with research and rehabilitation, hearing therapists, speech therapists, lip reading instructors, and acoustic physicists —are all interested in some aspect of audiology.

Basic testing of hearing is nowadays largely done with a pure tone audiometer. By pure tone audiometry is meant, as a rule, threshold testing of hearing with an audio-oscillator capable of producing 0 to 100 db or more of sound in a multiple tone, discrete, or continuous frequency spectrum. This is usually from around 125 cycles per sec. to 8000 cycles per sec., more or less. When discrete frequencies are used they tend to be in octaves; 128, 256, 512, 1024, 2048, 4096, and 8192 cycles is the old scale. A newer scale of 125, 250, 500, 1000, 2000, 4000, and 8000 cycles, which is essentially similar as far as the patient is concerned, is now more commonly used for technical reasons. Bone conduction measurements are made with the same instrument, using a suitable oscillator on the bone of the skull. In this country the audiometer has not only largely superseded tuning forks, but also live voice[2] and whispered tests, because it is so much easier to calibrate and use. There is usually incorporated in the instrument a calibrated buzzer type of noise maker to mask out the untested ear when necessary, and there may also be various switches and circuits and meters to provide calibrated microphone voice, alternate loudness balance, or difference limen recruitment measurements, and the like. It has been clearly demonstrated that the measurements of hearing must be done in a quiet place. The National Research Council (1) has urged that threshold measurements be done with the receiver in place in a room with less than 45 db of ambient noise.

[1] The survey of literature for this review was completed in June, 1955.

[2] The words "live voice" are often mistakenly used for "microphone voice."

The following brief review will give definitions of the technical terms used in this article. By "recruitment of loudness" is meant the hearing of loud sounds at a greater subjective intensity than would be expected from the threshold audiograms of a deafened ear. In the alternate balance loudness method of Fowler (2), for example, it was discovered that in many perceptively deafened ears, notably in Menière's disease, any sound 5 to 10 db above threshold was heard just as loudly in the deafened as in the normal ear. In Menière's disease this was the only indication of recruitment outside of the fact that it was known that, in the deafened ear, threshold measurements were always much more precise than in a conduction-deafened ear. Following this principle, Luscher & Zwislocki (3) developed difference limen tests using intensity modulation circuits in their audiometer. When a patient can differentiate minute intensity difference in the modulation, he is said by the authors to have recruitment. Patients with conduction deafness, such as those found in otosclerosis, or with middle ear adhesions, cannot as a rule detect minute changes in intensity modulation. In fact, in such conditions, the difference between the thresholds of the signal tone and intensity modulation tone may seem greater than the 2 to 6 db found in normal ears. Recruitment is probably a manifestation of the all-or-none law found in other nerves and has been observed in other sensory nerves. It is well brought out, in some of the articles here reviewed, that much must be learned about recruitment. It seems, as a rule, but not always, to indicate a lesion within the cochlea; therefore, its measurement tends to help differentiate between labyrinthine and retrolabyrinthine perceptive lesions.

The search has continued for a hearing test which will eliminate subjective responses. The simplest of these is still the old test of Aldrich (4). As may be remembered, he exposed small children to the sound of a whistle and then stuck their feet with a pin. It does not take an infant very long to realize that each time the whistle is blown he is likely to be subjected to pain, and he either pulls his foot away immediately after the whistle is sounded, or he begins to protest violently, or both. E. P. Fowler, Jr. has modernized this method somewhat by presenting a small electric shock, permitting the child to pull his foot against an elastic and away from the shock, as a reward for paying attention to the sound which is presented through audiometer headphones or a loud speaker. Other conditioning techniques, such as training a child to move blocks, place rings on a pole, or some other definite act, have also been successfully used for teaching children to indicate that they hear a sound. Similarly, puppets, dolls, and other toys can be used to indicate that the child hears the sound. These are called play techniques.

A few years ago, Bordley & Hardy (5) adapted the psychogalvanic skin resistance apparatus to a conditioning technique for the testing of hearing. This was widely heralded as the answer to the problem of making a child cooperate and respond to a test tone. Essentially, the technique consists of presenting a tone to a child through headphones or a loud speaker; immediately after this, a galvanic shock of mild degree is presented to the leg or some

other part of the body. Consciously or subconsciously, many children quickly learn that any presentation of sound may be succeeded by an electric shock. Fear of electric shock contracts their capillaries and changes their skin resistance; this can be recorded on a continuous ohmmeter with a suitably balanced Wheatstone bridge incorporated in a circuit which is attached to two electrodes on the skin. In most adults this method works very much as does a "lie detector" and is most useful in detecting malingerers and in persuading them to give accurate responses. With the children, however, it is not successful unless it is used by very skilled workers and much time is given to the test. Unfortunately, any psychic stimuli produce changes in skin resistance and therefore, in active or unco-operative children, there are so many false readings from stimuli other than the presentation of the sound that the records are then extremely difficult to interpret. Furthermore, with certain children, there is very little, if any, response to any sound or even to the electric shock. A warm room and calm, quiet surroundings are essential for use of this test. Even in skilled hands, there are 8 to 10 per cent of false positives and false negatives. The opinion of various writers concerning these techniques is given in the following pages.

There is also a discussion in this review of various types of audiometry. In the opinion of the reviewers, the pure tone audiometer described above has been, and is, the most satisfactory single device for accurately assessing, retesting, and following the hearing capacity of individuals of all ages. Speech varies so much from individual to individual, language to language, and from accent to accent, that it is easier, and probably fairer, even in compensation cases, to make measurements with an accepted reproducible method such as pure tone audiometry and then interpolate the speech, than it is to try to obtain direct measurements with speech material. Furthermore, it has been shown that, even under ordinary conditions, there is a remarkably fixed relationship between threshold-for-speech audiometry and the threshold-for-pure-tone audiometry (6). There are some who do not agree with these remarks, and this is brought out in the following paragraphs.

Other difficulties in audiometry have resulted from the lack of standards. It is generally agreed that, preferably on each audiogram and certainly in every article on the subject, reference levels and symbol meaning should be indicated. For example, if all audiograms had the notation, "0 equals average normal hearing [American Bureau of Standards (Beasley specification)]," or, "0 equals 0.0002 dynes per cm^2.," there would be less confusion than there is at present. Sometimes, both of the standard reference levels are used in the same audiogram, one for pure tones and the other for speech or masking. This is patently wrong. Similarly, if all individuals would chart their audiograms, using red for the right ear and blue for the left ear, it would be helpful. When preparing material for the printer, all writers should use a circle for the right ear and a dot or a cross for the left ear. There would then be less confusion in the reading of audiograms. Bone conduction should be charted on the same graph as the air conduction, with brackets "[" for the right and

"]" for the left, on each side of the line indicating the frequency used, and bearing in mind that each bracket represents the ear of the patient as he faces the examiner. This has been recommended for international use (1).

One of the most active and important fields in audiology at the moment involves the problems of industrial audiology. In Wisconsin and in the State of New York, many physicians, lawyers, and insurance carriers have been trying to develop an equitable law which would provide compensation for those who are deafened by noise in industry.

It is the opinion of these reviewers that general practitioners, internists pediatricians, and those engaged in medical practice in the Armed Services will eventually find it just as necessary to have audiometers in their offices to make measurements of hearing as it is to have a Snelling chart to make measurements of vision.

Case Findings and Assessment of Deafness in Children

The problems presented by the very young deaf, the mute, the inarticulate, and the aphasic are many. With the incidence of suspected hearing impairment, current research emphasizes the extreme importance of early diagnosis and assessment of the extent of the hearing involvement. The difficulties encountered vary with age, causes of deafness, the hearing test, and other tests to be administered. Wishart (7) recommends the testing of the newborn by means of a cowbell while the child is resting or sleeping. As he matures, the spoken voice, noise makers, and similar sounds can be used. McLaurin (8) prefers the use of noise makers in a free field, rather than pure tone audiometry, psychogalvanic skin response following conditioning to an electric shock (known as PGSR), peep-show, or electroencephalograph. These, he feels, are not proper for the diagnosis of speech defects and hearing defects of young children. He concludes that a better diagnosis can be accomplished by detailed history-taking, clinical observation, and clinical evaluation. However, Barr (9), in his experiments with 300 children from the ages of one to six years, used both the PGSR and play audiometry. Except for a difference of not more than 5 db, the two methods were in full agreement in 85 per cent of the threshold investigations. A follow up examination, one to two years later, showed practically unchanged audiograms. The writer expressed a preference for play audiometry, because it was a pleasant experience as compared to the relative unpleasantness necessitated by the electric shock of the PGSR. In a comparative study of pure tone audiometry and speech audiometry, Sortini & Flake (10) report that conventional pure tone audiometry is time consuming, unreliable, and does not investigate the "level at which a child lives with his impairment." They preferred giving the child toys which correspond to certain familiar spondee words, i.e., cowboy, airplane, etc. A spondee-repeat threshold is established when the child points to, and repeats, the word. These tests were administered both in free field and with earphones. Such a test procedure insures a high degree of subject co-operation and a relatively short administration time in young children

who are extremely difficult to test. A similar testing procedure was reported by Siegenthaler and his associates (11) in which a picture identification technique, with carefully selected stimulus words and pictures, was used. With children as young as three and four years of age, a high correlation between pure tone averages as measured with a conventional audiometer, and speech reception threshold, was reported. The two forms of the test are essentially equal.

A presentation which covers the differential diagnosis in children with communication disorders was made by Kastein & Fowler, Jr. (12). A study of 156 children, who were suspected of having a hearing loss because of impaired or absent language or failure of speech development, was made. The results indicate that 54 had a peripheral hearing loss; 27 had a peripheral hearing loss and brain injury, mental retardation, or emotional disturbances; and 75 had no peripheral hearing loss of significance. In these latter cases, central imperception or mental illness was the causative factor in the nondevelopment of speech. A discussion is given of the development of a practical clinical method to obtain a reliable diagnostic impression through a specially designed language and speech evaluation. The need for adequate training in language, at an early age, is stressed. It is emphasized that many children with slight hearing losses are classified and treated as deaf when this is entirely unwarranted. Proper facilities for the detection and care of those children who have been found to have multiple handicaps are urged. McHugh & McCoy (13) carried out a study to evaluate a method of investigation, recommended by Myklebust, for children who are suspected of having impaired language because of deafness. They conclude that Myklebust's method is practical in differentiating the deaf child from those whose lack of speech is due to some form of central damge or dysfunction. (This method recommends analyzing the child's total behavioral pattern, rather than assessing only the child's response to sound.)

Irwin & Shreve (14) in reporting on a study to determine the gains in language adjustment to amplified sound with a group of four-to-six-year-old hard-of-hearing children, conclude that this group can be trained to respond both to pure-tone and free-field speech testing. They found that children who are enrolled in a hard-of-hearing training program will show gains in language ability when fitted with a wearable hearing aid. Consistent auditory training will help in the adjustment to a hearing aid. The effectiveness of auditory training for profoundly deaf pupils in a residential school for the deaf was shown by Hudgins (15). It was concluded that the constant use of a powerful, high fidelity, group hearing aid throughout the day is of considerable benefit to deaf children with a measurable benefit in increased communicative skills. The profoundly deaf need high-powered equipment, capable of presenting undistorted speech signals. Sound-treated, quiet rooms are desirable in schools for the deaf to exclude amplified unwanted sounds.

Several significant studies have been made concerning the incidence of hearing loss in children. Pauls & Hardy (16) reported on 572 infants and pre-

school children with communication disorders. Complete audiological studies (PGSR) with good test-retest reliability, and complete psychological and pediatric investigations were performed. The results show that one-fifth had normal hearing, and four-fifths had impaired hearing (18 with conductive lesions and the remainder with a nerve or mixed type deafness). One-third of the lesions were ascribed to prenatal difficulties, two-thirds to postnatal. The authors state that the most important single factor in the prognosis and handling of children with communicative disorders is to estimate the potential speech-hearing threshold (unaided). Kinney (17), in analyzing 2628 deafened children, found a ratio of 2:1 of conductive to perceptive losses. He states that the measles virus, as a cause of perceptive deafness, is more important than previously reported. In a report of 295 children in Copenhagen (18), Falbe-Hansen found that in 21.7 per cent of the cases the deafness was perceptive and in 78.3 per cent it was conductive. Of this latter group, 90 per cent improved with treatment. In the more socially favored sections 9.7 per cent had defects, whereas in the poorer sections 15.5 per cent were found to be involved. Johnsen (19, 20), in a study of 111 children with high frequency perceptive deafness, found that maternal rubella or congenital syphilis is only rarely found as the cause of symmetric perceptive deafness. He reports that 40 per cent of the perceptive deafness is of a genetic origin. He concludes that, in most instances, the lesion is transmitted either by irregular dominant or by recessive inheritance. Exogenous factors were found in about one-half of the non-hereditary types. Erythroblastosis was the cause of the lesion in about 5 per cent of the cases; 10 per cent were due to paranatal asphyxia; and in another 10 per cent, the perceptive deafness was related to prematurity without demonstrable signs of asphyxia. In one-third of the cases the cause could not be demonsrrated. Slightly different figures are given by Fowler, Jr. & Basek (21), who stress the importance of the first trimester of pregnancy in the occurrence of congenital defects.

Tests for Malingering or Psychogenic Deafness

Since the need for an objective measure of hearing is so necessary in the clinical evaluation of malingerers, psychologically deafened, very young children, and children suffering from communication disorders, the study reported by Goldstein and his associates (22) on an attempt to examine the applicability of the psychogalvanic skin response test (PGSR) to the clinical testing of hearing in children is significant. Children who appeared to suffer from some communication disorder other than, or in addition to, peripheral deafness, were studied. Those children, who were difficult to condition, showed audiometric results which suggested poorer hearing than was indicated by conventional tests, and thus the authors conclude that the PGSR test procedure may serve to confirm a clinical diagnosis of communication disorder other than peripheral deafness. In summarizing their investigations Goodhill *et al.* (23) recognize that the development of PGSR audiometric testing is a significant achievement; however, they feel that the interpreta-

tions of the findings are valid in small children only when they are compared and evaluated with other types of auditory testing, i.e., startle reflex, and the pure tone audiometer. They conclude by stating that these are nonobjective tests and the search for a truly objective test must continue. Stewart (24) reports on a new instrument for detecting the galvanic response and finds that its advantages over the older instruments are that it is selective, requires no manipulation during use, and provides a chart record that is easier and more positive to analyze. However, he states that the instrument alone does not give complete objectivity to the technique in the study of hearing sensitivity, but rather such objectivity will come about only through the application of the instrument in a proper experimental method. Stewart (25) reports on the application of his suggested techniques using 15 subjects, ranging in age from 17 to 30, with normal hearing. His experimental design employs conditioning criteria, controls, and an objective definition of response in an overall procedure that avoided subjective judgment. He concludes that PGSRs to acoustic stimuli can be discriminated from other stimuli with an extraordinarily high degree of significance, with the use of his method, and for the group tested. Using Stewart's criteria for defining the skin response to galvanic electric shock conditioning and similar equipment, Doerfler & McClure (26) used 30 subjects with hearing losses. They report that the 1000 cycle threshold of hearing for adults with conductive hearing loss can be determined in an objective manner by improved instrumentation and proper design in the use of the galvanic skin response.

Tests for malingering, cases of psychogenic deafness, aphasics, and others still present the greatest area of challenge in audiology. The eye-blink response as a test for hearing has been proposed by Galambos and his associates (27). A sound wave generator and earphones for production of clicks, a crystal phonograph cartridge on the eyelid, and an oscilloscope for recording the blinks, are used. At about 50 db above threshold, blinks begin to occur when clicks are presented. At 130 db above threshold, blinks occur every time clicks are presented. This test does not clearly differentiate organic from nonorganic, or conductive from nerve type losses; however, subjects with hearing losses will respond as normal subjects except that higher intensities of sound are necessary to produce blinks in deafened subjects. This test is presented as an aid to the detection of certain types of malingering. Jepson (28) uses an acoustic measuring bridge, a tone generator, and an audiometer. In his method of acoustic examination, the impedance of the ear not under test, due to contraction of the intratympanic muscles which contract in sympathy with the ear being stimulated, is used as an indicator of acoustic function. This is said to have the advantage of being a purely objective hearing test. Hanley & Tiffany (29, 30), in discussing all the current tests for nonorganic hearing loss, feel that the need for more reliable examining procedures for this type of hearing loss still exists. After some five years of research they offer their test which involves the use of the "delayed-side-tone phenomenon" as approaching, more adequately, the criteria for a malinger-

er's test. They emphasize that, although failure on the delayed-side-tone test probably establishes the integrity of the peripheral auditory mechanism, it does not necessarily establish malingering as a diagnosis. Heller & Lindenberg (31) recommend the study of the entire patient: his complete medical and social history, his behavior, his speech, and his physical status. These, with adequate testing of auditory function, should produce competent conclusions regarding the patient with a deafness of nonorganic origin. In addition, the motivation for malingering or psychogenic deafness must be uncovered by psychiatric investigation. In a summary of current tests for malingering which are now being used, Glorig (32) states that malingering cannot be demonstrated by hearing tests alone. It must be differentiated from hearing losses of psychogenic origin by obtaining, either directly or indirectly, an admission of intent to defraud. There is great need for tests which will differentiate and delineate functional losses and others due to hysteria, malingering, or pure psychological causes.

Measurements of Hearing Above Threshold

The measurement of the difference limen of intensity as a means of determining the extent of recruitment, and at the same time of locating the cause of a hearing loss, is creating more and more interest. Meurman (33) describes the procedures by which a second tone generator was connected to the continuous frequency self recording Bekesy audiometer, thus making it possible to follow the difference limen of intensity (DLI), at a single frequency, as long as is desired. An octave frequency audiogram is obtained by varying the frequency at short intervals in octave steps. In certain cases, the DLI can be read more easily from this audiogram than from the on and off swings of a Bekesy curve. Lansberg (34), in an excellent comprehensive survey of recruitment in various types of disorders and testing techniques, concludes that the importance of the recruitment phenomenon in diagnosis and therapy is that differential diagnosis, in cases of perceptive deafness, can usually be based on the absence or presence of recruitment, and that it is important in the prescription of hearing aids. The recruitment phenomenon has deepened our insight into the mechanism of sound perception. Recruitment testing is one means of revealing the intricacies of fatigue, adaptation, and trauma. Markle (35) suggests that there may be a possiblity that recruitment is not an indication of any type of nerve lesion but is, rather, an indication of a pseudo nerve lesion, or a conductive lesion within the inner ear. He proposes that perhaps recruitment is an indication of a potentially reversible "conductive lesion within the inner ear." Bangs & Mullins (36) provide a very informative article concerning existing techniques for testing the presence of recruitment. On the basis of comparisons of the range of loudness, Bekesy audiometry, the Luscher-Zwislocki test, and the Denes-Naunton method, the authors conclude the range of loudness method was the most discriminating technique with the loudness-to-threshold method easily the best of the three measures. The authors cite the characteristics of

a good recruitment test: it must be as valid as possible, it should be applicable to all types of hearing losses, it should be inexpensive, and it should be simple to administer and interpret. In a report made by Hirsch and his associates (37) on an experimental study of 44 students with a variety of types of hearing losses, and of 18 normal subjects, it was established that the difference limen did not distinguish recruiting and nonrecruiting cases. Nor did the difference limen distinguish hard-of-hearing listeners from normal listeners when the difference limen was measured with discrete tones at sensation levels of 5, 25, and 40 db relative to the person's threshold. Although the authors state that there may be some relation between the size of the difference limen, under certain procedures, and the presence of recruitment, the relation is so dependent on features of the procedure that a single difference limen technique cannot yet be recommended for general clinical use. This is unfortunate, because we need tests other than the measurement of bone conduction and loudness balance testing for the differential diagnosis of the various types of deafness.

Speech Audiometry

Cawthorne & Harvey (38) studied 350 patients with various types of hearing losses, including post-fenestration operation hearing losses, and found that in 150 conductive deafness cases the speech audiogram gave little more information than the pure tone audiogram. In cases of perceptive deafness, the ability to understand speech seemed to bear little relationship to pure tone thresholds (particularly in Menière's disease and traumatic deafness cases). However, in those cases where the nature of the lesion is undetermined, there is not always a disparity between speech and pure tones. For example, in discussing favorable post-fenestration cases, they found that improvement for speech corresponds to improvement for pure tone thresholds. Knight & Littler (39) describe the technique of speech audiometry and the design of a simple speech audiometer with a masking generator. The techniques to be used in conductive and perceptive deafness, selection of hearing aids, instructions to technicians, and word articulation tests are included. Walsh (40) suggests that adequate speech audiometry can be done with a speech audiometer and records in the otologist's office. He discusses the test procedure for establishing thresholds and obtaining discrimination scores, and to evaluate what he calls "the social adequacy index of hearing." He states that speech testing is more satisfactory than pure tone testing in predicting possible results from fenestration. Speech audiometry is also useful, he believes, in the differential diagnosis of Menière's disease. He found that, with speech tests, the discrimination score was universally low in classical cases of the disease. It would seem that a poor discrimination score for speech, with relatively small threshold loss for speech, is indicative of an end organ lesion. Bocca, Calearo & Cassinari (41) have devised a method of speech audiometry, using distorted speech, which will indicate the "hidden" auditory loss in temporal lobe tumors.

Since, from their material, the articulation score has proved to be much poorer in the ear contralateral to the side of the tumor, the authors assume that, when the auditory cortex is involved by the growth, the psychic integration of the verbal passage may be more or less impaired.

Masking, Fatigue, and Bone Conduction

The effects of masking and fatigue with white noise in connection with speech tests in otosclerotic subjects were reported by Sambataro & Pestalozza (42). Using six subjects in comparison between normal and otosclerotic ears for low intensity levels of white noise, the shift is far lower in otosclerosis; for higher intensity levels of white noise, the shift is the same for both normal and otosclerotic subjects. After 15 min. of exposure to 60 db of white noise, the articulation curve of the otosclerotic ear does not improve, whereas the normal ear does improve slowly. Farrior and his associates (43) state that the current investigation in fenestration surgery is designed to reduce postoperative serous labyrinthitis. For the evaluation of postoperative serous labyrinthitis, the following criteria are proposed: (*a*) presence or absence of primary improvement, (*b*) degree of secondary variations in bone conduction as manifested by shifts of lateralization, depression of threshold diplacusis, or recruitment, (*c*) the time and degree of tertiary improvement in bone conduction, (*d*) the six week improvement in air conduction for high frequencies and for the usual speech frequencies, and (*e*) the incidence of terminal nerve deafness. Henner (44) studied 72 postoperative fenestration cases. Since eight had both ears operated on, a few of the cases were more than five years post-fenestration. He found that bone conduction seemed to improve in cases which, preoperatively, had a dip in bone conduction at 1000 and 2000 cycles and in which the postoperative result was better than 25 db for speech. Bone conduction also improved in about 50 per cent of the ideal cases. Regarding the prediction of postoperative hearing, Henner suggests it should be qualified as to the type of case. Using the Shambaugh-Carhart classification of three classes, he believes Class I, since there is usually a 23 db average for the speech frequencies postoperatively, does not merit using a bone conduction factor in trying to make a predicted result of 30 db or better (plus or minus 10 db). In Class II, successful hearing may be predicted if all other findings indicate an ideal case: relative good air conduction in the upper frequencies, excellent speech discrimination scores, and good bone conduction at 4000 cycles. In Class III, the resultant hearing gain does not merit the fenestration operation, although the bone conduction may improve similarly to Class II. Class II and III predictions are of value to the surgeon in classifying cases, and to the patient in understanding the kind of hearing he may expect. Rytzner (45) is the author of a comprehensive monograph in which the exposure effects of blocking and surgery on hearing acuity in the otosclerotic ear are thoroughly investigated.

Miscellaneous Tests for Hearing Function

Other tests of hearing ability include directional free field startle reflex audiometry which was reported by Goodhill (46), who modified the startle reflex audiometric technique with the addition of attenuation and four loud speakers in different corners of the room for directional responses by the subject. The directional responses, so obtained by utilizing ocular or head movements as a criterion for awareness of the sound source, give additional information and are particularly helpful in testing children. King (47) states, in his study of free field voice tests using both spoken voice and whisper, that the imperfections of these tests are so extensive that he suggests that they should be replaced by conventional pure tone audiometry.

Kobrak (48) reports the use of two tracer substances, cigarette smoke and minute fibres of cotton, as a means of visualizing the role of the intratympanal air in sound conduction. These experiments prove the feasibility of using mechanical indicators for the study of air vibrations.

Hoople *et al.* (49) have reported the effects of masking air conduction and bone conduction, using irrigation of the ear canal water douche method which produces a masking in the order of 90 db for air conduction and 45 to 50 db for bone conduction measurements. It is anticipated that water douche masking may be less likely to result in spurious elevated threshold readings for an unmasked ear than the more universalized high intensity noise masking. Bone conduction tests were administered with and without wax plugs by Everberg (50), who concluded that the "improvement" of bone conduction seen in certain of conduction deafnesses is based on the relative deafness of these people to the surrounding noise. The improvement of hearing for bone conduction after occlusion of the meatus was an absolute phenomenon. Reporting on acoustic attenuation between ears, Zwislocki (51) states that intraotic insulation increases as the area under the earphone decreases, and is greatest where the sound is introduced into the ear through a perforated ear plug, which gives the smallest effective surface for bone conduction. This is true, though, only when it is possible to eliminate most of the sound radiation into the air surrounding the head. The author feels that we will be able to build an earphone which will almost eliminate intraotic leakage, thus eliminating the necessity of masking the other ear in order to obtain correct measurements of monaural hearing. Another aspect under study concerning bone conduction testing is that of improving the manner in which the vibrators are coupled to the skull. Harris *et al.* (52) have mounted the vibrator in a helmet. They found that the helmet significantly reduces variance among bone conduction threshold measurements obtained over long periods. Weille & Gargano (53) confirm Bekesy's theories of bone conduction and state that no unmasked bone conduction audiometry is valid if both ears are functioning; proper quantitative masking will prevent false readings as a result of over masking. The index of true function by bone conduction should be the average of the best scores obtained over a

period of time, checked by using speech audiometry at high sound pressure level.

Palva & Goodman (54) show that the thresholds for pure tones between 250 and 8000 cycles per sec., when taken in the presence of white noise at 100 db in the same ear, will be very close to one another at the lower frequencies and within 10 db of each other at higher frequencies. It was concluded that "masked threshold" is not a useful indicator for differential diagnosis, because a flat audiogram was always obtained in the presence of noise. Simonton & Hedgecock (55) state that loss of hearing, due to middle ear conductive deafness, does not reduce discrimination of speech in noisy environments; losses of the perceptive type result in moderate loss of discrimination in noise. However, wide variations in individual discrimination were noted, both with and without noise. Pestalozza & Lazzaroni (56) found that noise produces an obvious threshold shift in normal hearing subjects, those with conductive deafness and those with experimental distortions exhibiting a rising audiometric curve. These authors conclude that noise produces the threshold shift, whereas distortion determines the decrease of the articulation score with an increase in intensity.

Juers (57) cites several cases in which reversal of an early end-organ deafness was observed. He believes that the failure of both ears to improve indicates the lesion has progressed to a stage of irreversibility in one ear. It is possible that, in some instances, there was a spontaneous reversal of the lesion. The author states that a broad physiological approach to a wide range of etiological factors is perhaps most important in the interpretation of these cases. Dix & Hood (58) review recent papers discussing "nerve deafness," "fibre deafness," and "end-organ deafness," with particular stress on the technique of testing procedures. They report on two cases of neurofibromas in which there was no change in hearing from preoperative to postoperative testing, but there was a change from over-recruitment to the absence of recruitment. They conclude that this lends support to the theory that it is interference with cochlear blood supply which is the chance factor responsible for recruitment.

Rehabilitation and Standards for Hearing Centers

The Committee on Minimum Requirements for Hearing Clinics of the American Speech and Hearing Association (59) list the following as minimum requirements for hearing programs offering guidance in selecting hearing aids: (*a*) Patients should have otological guidance and diagnosis, medical or surgical treatment as indicated, and facilities to make ear impressions should be available. (*b*) Personnel should have clinical certification by the American Speech and Hearing Association. (*c*) Testing rooms should have calibrated equipment; electro-acoustic and other equipment should meet conventional standards of accuracy (the minimum equipment should provide measurement of thresholds for pure tones, and threshold and supra threshold for speech). The hearing program should provide for

the education and rehabilitation of the persons examined, and should include a stock of currently available commercial hearing aids. It should adhere to sound ethical practice as set up by the American Speech and Hearing Association code of ethics, and should refer only to "acceptable" organizations or companies. (Unfortunately, the Subcommittee of Hearing Aids of the AMA has ceased reporting on the acceptance of hearing aids and the ethics and financial reliability of companies selling hearing aids and audiometers. A suitable substitute should be found for this service.)

The problems presented by the hard-of-hearing must be solved by a multifaceted approach. Prevention of deafness and conservation of hearing must include the otologist. Fox (60) admirably details such a role in an industrial program. Guilford (61) is of the opinion that hearing rehabilitation is an integral part of otolaryngology in private practice. He suggests an otologist-audiologist team whose function would be to diagnose the hearing handicap and to advise and administer the appropriate therapy. He includes a description of facilities, personnel, and hearing tests commonly used in private rehabilitation practice. Hoople & DiCarlo (62) list, in order of importance, the otologist and other personnel, housing, and equipment in their suggestions of forming a hearing and speech center. This is a comprehensive article which is of great value to those who are setting up a center.

Since case finding is the major consideration of any extensive program of hearing rehabilitation, the description by DiCarlo & Gardner (63) of the readapted Johnston pure tone screening test, which was administered to college students, is significant. They conclude that, in terms of time, cost, and results, mass pure tone group testing is an efficient means of testing university populations. Lindenberg & Fowler, Jr. (64) believe that screening tests with conventional pure tone audiometers in a quiet place or sound proof booths are both more accurate and more economical than group tests for schools, universities, and industry.

Effects of Noise on Hearing

Physicians are becoming more and more cognizant of the problems of industrial noise and its resultant deafness. In a survey by Fox (65), it was found that 64 workers out of 102 had a measurable hearing loss proportionate to the length of time of employment. The number of years of exposure to noise, rather than age of employee per se, was the important factor in the incidence and severity of deafness. Goldner (66), in a critical evaluation of deafness in 600 shipyard workers, found, on the other hand, that the length of employment (except for very prolonged periods) apparently did not result in a proportion of greater loss for greater length of employment. His studies indicated that older employees were probably not more susceptible to acoustic trauma; rather, the workers who were most intimately connected with the noisy process or who worked in the most confined spaces showed the greater hearing losses. A predominant loss for higher tones was noted; however, occupational deafness often seemed to co-exist with early or late con-

ductive deafness. Other problems such as burns of the external canal or tympanic membrane, perforations, or traumatic deafness due to injury, may be present with traumatic deafness. The author suggests, as preventive measures, recognizing the hazards, pre-employment examinations and audiograms, improved industrial design and sound proofing, and medical control of exposed workers—not only for excessive noise, but also for other possible injuries to the acoustic mechanism.

Larsen (67) discusses prophylaxis as a means of reducing the incidence of occupational deafness. Individual prophylaxis consists of selection of workers and protection of the ear; general prophylaxis concerns technical procedures to reduce high noise levels at their origin, and arranging for intervals of rest in quiet surroundings for those who must necessarily be exposed to high intensities for prolonged periods.

Ruedi (68) states that, on the basis of experimentally produced histological changes in the animal ear and temporary deafness in the human ear, pure tone trauma and noise trauma produce different effects. In the stage of noise trauma, as in pure tone trauma, the transition from physiological fatigue to pathological fatigue or stimulation deafness occurs abruptly above an individually varying critical intensity for white noise. This may be of some importance when measuring to eliminate noise in industry is being considered.

Sataloff (69) studied 272 subjects who were daily exposed to a steady stated noise (jet engine between 90 and 120 db) for a five year period. Of the 153 subjects used, he concluded that steady state jet engine noise between 90 and 120 db, with sound energy below 600 c.p.s., is not detrimental to the average subject. After the exposure, there was no change in hearing for 1024 or 2048 cycles; there was no change greater than 30 db for 4096 or 8192 cycles. Tinnitus and subjective hearing losses were rarely encountered and, if they did occur, were not related to the frequency or intensity of the noise being investigated. Finally, he concluded that it would appear that the human ear is more resistant to injury by noise than is usually thought to be the case.

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DISEASES OF THE BONES AND JOINTS[1]

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In this chapter, disorders of the bones and joints are reviewed primarily from the standpoint of an orthopedic surgeon. Although some attempt has been made to incorporate material of interest to all physicians, the field is so broad and publications so numerous that it is impossible, in the limited space permitted, to cover the field completely.

Poliomyelitis

Poliomyelitis may be said to have aroused the greatest interest of the year in all of medicine, among laymen and physicians alike. It may be considered logically as one of the diseases of the bones and joints, for although it is a central nervous system disease it leaves its greatest impact on the muscles; the resultant inability of its victim to use his joints and bones catches the eye of the general public.

Because of the early confusion regarding the usefulness and dangers of the Salk vaccine, we cannot hope to be completely up-to-date at the time this review is published. Shortly after the publication of a bulletin (1) by the United States Public Health Service, a critical review of the whole situation became necessary. As the year progressed, however, there seemed to be increasing confidence in the vaccine. The situation prior to introduction of the vaccine was well reviewed by Van Riper (2).

Muscle recovery following poliomyelitis was discussed by Sharrard (3). A standard scale of muscle power is used, modified as follows: 0 = no contraction; 1 = trace of contraction; 2 = active movement with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and some resistance; 5 = active movement against gravity and considerable resitance; 6 = normal power. Then if 2 is added to a muscle's grade in one month and 1.5 at two months, 1 at four months, and 1 at six months, a final grade in the muscle can be estimated at any time. It appears that the improvement in muscles weakened by poliomyelitis is predictable if paralysis is carefully assessed within one month of the onset of the disease. He stated that a key to the understanding of muscle recovery in poliomyelitis is found in a division of the paralyzed muscles into recoverable and irrecoverable fractions, whose proportions are determined in each case by the site and extent of the motor nerve cell destruction that has occurred during the acute stage of the disease and is the factor governing the general severity of the paralysis in an epidemic, in a patient, or in a limb, and which is responsible for the apparent differences in the power of recovery of different muscles. When the irrecoverable fraction—that is, the muscles which have

[1] The survey of literature pertaining to this review was completed in July, 1955.

suffered complete and permanent paralysis by loss of all the motor nerves supplying them—is separated from the remainder, the true picture of muscle recovery can be seen.

Sharrard's studies involved about 5000 muscles in 142 patients. The clinical differences in the ability of individual muscles to recover depended upon the proportions of their number that remained permanently paralyzed. The rate of recovery was more rapid in children than in adults, and the prediction could be made any time after one month following onset of the paralysis that about 93 per cent of total muscular recovery would take place by the end of the twelfth month and full recovery by the end of 24 months. About 90 per cent of the muscles still completely paralyzed after six months remained so permanently. Deterioration in power of a muscle is common, and when it occurs it is associated with the presence of strong opposing forces of antagonistic muscles, or of gravity.

Sharrard's summary emphasizes for us, and especially for those who treat the patient with acute poliomyelitis, the fact that we have been properly managing such patients having anticipation of recovery for a period up to one year in most instances; that we have been able to predict the progress of an individual with poliomyelitis fairly well after one month following the acute onset; and that we have felt further treatment in a concentrated form (such as muscle re-education, muscle-building exercising, and stretching) was often not necessary for more than six to twelve months.

The report of the British Orthopedists Association on Poliomyelitis (4) is of particular interest. It states that before the First World War, orthopedic surgeons usually saw patients with poliomyelitis only after the deformities had developed. They were seen in out-patient clinics as cripples who required operative correction for the deformities that had developed following loss of muscle balance. Improved legislation enabled children who suffered from poliomyelitis to come under more comprehensive treatment in newly organized clinics which served as links between the orthopedic hospitals and infectious disease hospitals, with orthopedic supervision instituted in the acute stage of the disease and continuity of treatment assumed after the patient was transferred to an orthopedic hospital or to his home. The article states further that an orthopedic surgeon is informed immediately upon admission of the patient with poliomyelitis to the infectious disease hospital, ensuring adequate early treatment of paralysis during the most important initial stages wherein contractures often develop rapidly. This leads automatically to continuity of treatment and rehabilitation throughout the whole phase of recovery, including the patient's training and settlement into a suitable occupation. It was suggested that the plan whereby the Orthopedic Services are engaged from the beginning should be adopted on a nationwide basis in the British Isles.

Important points of differentiation between poliomyelitis and the Guillain-Barré syndrome are nicely discussed by Mulroy (5). He states that, unlike poliomyelitis, the etiology of the Guillain-Barré syndrome is unknown.

The latter is non-seasonal, occurs in all decades of life, and is non-epidemic. In more than half of the cases there is antecedent infection, usually of the upper respiratory tract, followed by a latent period. The temperature is usually normal, and there are no signs of infection when neurologic symptoms occur. Poliomyelitis is accompanied by fever, systemic infection, and rapid onset of paralysis. Sensory changes are rare in poliomyelitis, while they occur frequently in the Guillain-Barré syndrome. Vasomotor changes meningeal irritation, and headaches are frequent in poliomyelitis and rarely seen in the other state. The motor symptoms in the latter are bilateral, symmetric and ascending, and the paralysis may progress for days or weeks, whereas the paralysis of poliomyelitis follows no pattern, with additional involvement rarely occurring after the second week. Optic neuritis, diplopia, and involvement of the ninth and tenth nerves are frequent in both disorders. However, facial paralysis is as frequent as 50 per cent in the Guillain-Barré syndrome. Spinal fluid in the latter has a high total protein with few cells, whereas in poliomyelitis there are many cells and only slightly elevated total protein. With extensive involvement, the prognosis on poliomyelitis is poor, while in the Guillain-Barré syndrome the possibility of functional recovery is good although some series report as much as 20 per cent mortality. Thus an important differentiation is to be made between these two diseases, and certainly the two should not be confused.

Friederwitzer's report of one case of the Guillain-Barré syndrome (6) is of particular interest because of the quotation from the original report of Guillain and Barré, defining the disease as "acute diffuse infective disease of the nervous system, involving the spinal cord and peripheral nerves and occasionally the brain." This original definition has had to be revised somewhat, because of the realization that it at least is not a recognizable infectious disease.

Congenital Deformities

The treatment of congenital deformities is still an ever present problem, and various methods are being developed from time to time which seem to improve the chances for completely and more rapidly overcoming the difficulties of congenital dislocations of the hip, of internal tibial torsion, congenital club feet, etc. In a typical paper (7) that presents this problem the authors present particularly the use of the Hilgenreiner splint, and, in some instances, the use of the Denis Browne appliance. Chuinard (8) stresses the use of skeletal traction, derotation osteotomy, and early weight-bearing to correct congenital dislocation of the hip with anteversion.

These are only two of many different articles on the present treatment of congenital dislocation of the hip, and their recommendations vary to some extent from the type of treatment that this author and some of his associates have been practicing for a number of years. We have been using a reduction in the frog leg position, insofar as is possible, with or without the use of an adductor tenotomy done in the cast room through a $\frac{1}{4}$ in. incision. This is a

blind tenotomy, and has been performed successfully without injury to any adjacent structures. The usual frog leg position is maintained, and a cast is applied from the lower calves upward to the nipple line about the body. Such a cast is used for 6 to 12 weeks, and is then replaced by one on just the legs including the feet and ankles and up to the groin connected with crossbars. The frog leg position is then modified somewhat with more adduction of the hips, but the knees are maintained with some flexion. Gradually internal rotation is accomplished with cast changes at 4 to 6 week intervals. Some traction on the hips is obtained as a consequence of the weight of the cast on the lower extremities. The parents are instructed to carry the youngster under the arm pits and about the upper body, allowing the cast to dangle as far as possible. Some dragging and pulling of the casts results also as the youngster crawls about, pulling himself forward with his hands and dragging the cast behind him. Our observations to date show that apparently there has been a more rapid build up of the lateral acetabular margins. We suspect that this may be the direct result of the pull of the capsule along the lateral margin of the acetabulum, resulting in more rapid production of the bone at this point, and thus producing a deeper acetabulum and even a sort of a shelf at the lateral margin of the acetabulum.

Rudin (9) discusses the conservative management of congenital clubfoot deformity. Emphasis here has been placed upon the use of the Denis Browne splint, hoping by the active use of the extremities to take advantage of dynamic forces and so effect correction more rapidly. He reviews the use of this splint and that of corrective shoes and of other apparatus as well.

In a review of torsion of the legs in children, Kite (10) states that bowleg and knock-knee in infancy are often misdiagnosed and incorrectly treated as rickets. He emphasizes once again the fact that there is such a deformity as medial torsion of the tibia and fibula, and points out that this condition is often unrecognized until the youngster stands and walks, when the feet are noted to be adducted suggesting a metatarsus varus, and when the child sits with the knees flexed, the feet are adducted with the toes pointing inward. The bow-legged deformity is apparent rather than real, because the youngster tends to allow the toes to point straight forward only by permitting the legs to roll laterally from the hips with the patellae pointing laterally 45° or more. For this he advocates exercises, and, if no result is obtained in a few months, the use of a metal bar attached to the shoes to be worn in bed at night. He emphasizes the fact that sleeping in the prone position during the first months of life often seems to influence lateral torsion and lateral rotation of the feet and legs, and suggests particularly that the sleeping youngster should lie on his side or back. A cross bar with the toes pointing in, attaching shoes to the cross bar, serves to overcome this deformity.

Bone Grafting

Chronic bone infection has been treated in various ways in the past. In a recent report (11) it is stated that extensive pyogenic bone infections resulting from gunshot wounds, compound fractures, etc. may be eradicated by

excision and grafting of the skin directly, using a split thickness graft to cover the bare bone and tissues by suturing to the wound margin as a primary stage. As a secondary stage, the graft is removed and the bone surface is freshened by curettage, with a pedicle graft of skin and subcutaneous tissue added later. In some instances the second stage was found to be unnecessary, provided there was sufficient bone for strength of the extremity underneath. The split thickness graft often tended to form a fibrous connective tissue beneath it, which acted as a tough resilient bone covering.

Of great interest to medicine in general, and its reconstructive phases in particular is the work of Rosenberg, Reich & Brahms (12), who filled in bony defects by the use of milled bone. The term "milled bone," as used here refers to bone that is actually ground to sawdust like consistency and is then implanted to fill bony defects. It is also placed around fractures and weakened areas in bone as a readily used substance for the more rapid repair and filling of these bony defects. This procedure has been reported et the American Academy of Orthopedic Surgery Meeting in January 1955 at Los Angeles, and again in February, 1955 in Cleveland at the American College of Surgeons, Orthopedic Section. It is of considerable interest in that if offers the use of cortical rather than cancellous bone. The cortical bone is carefully washed early in the trinding process, on the premise that the particular value of this procedure is that in this initial washing much of the fatty substances are washed away, with consequently less tissue reaction locally at the site of the bone grafting. Various types of kitchen blenders have been used for this work. Milled bone has proved of use to the author in about 7 to 10 cases wherein it appears to have enhanced the bone healing process. The use of autogenous bone apparently produces better results than bank bone, although we have used both. This is in accordance with the reports of Rosenberg *et al.* (12).

The author has varied the method somewhat, as follows. When using milled bone, he has tried to surround the bone shaft with a small sheet of catgut after filling in the bone defect with finely milled bone. The catgut, regularly perforated at intervals to allow leakage of blood, etc., acts like skin on a sausage. This has proved effective, and has not resulted in too much tissue reaction to date. In other instances where there has been a one-sided bony defect, in which it was difficult to lodge and maintain the milled bone in its proper position, the author has used the sheet catgut by suturing it to the soft tissues below, pouring in the milled bone and suturing the catgut to the soft tissues above as well. In several instances, we discovered that the milled bone became almost concrete-like because of its ability to be packed down and dried out. As a consequence, we have mixed whole blood taken from the patient with the milled bone just prior to its insertion.

In reconstructive operations there have often been failures in the use of free bone grafts from the patient or from other sources, whether the donations be from bank bone or live bone. The situation has been long studied. Hardly any large orthopedic meeting is held without some discussion of muscle pedicle bone grafts and comparisons of other sources of bone. Davis (13)

describes such a one, and Hartley & Silver (14) describe several types of muscle pedicle bone grafts. Davis, reporting on nine patients, obtained successful bone hip fusion in eight, and presented adequate reasons for failure in the ninth case. Of interest is the fact that the average time for bony ankylosis, disregarding the unsuccessful graft, was 13 weeks, which is considerably shorter than the average we find for this type of operation. Hartley & Silver (14), on the basis of experimental work with rabbits, suggest that muscle pedicle grafts are more effective in maintaining life in the grafted bone.

Siffert (15) sums up past findings on experimental bone transplants. Transplants of autogenous bone are incorporated more rapidly than homogenous grafts. The healing of a bone defect in the presence of a fragment of transplanted bone is similar to the healing of a fracture. Small transplanted fragments are surrounded, invaded, and replaced by new bone more rapidly than are larger fragments, purely as the result of their architectural features. Despite the apparently transient rôle played by the grafts, they are thought to represent a determining factor in the healing across the bone defect. The experiments also support the concept that transplants serve primarily as a passive scaffolding along which new bone may grow. Invading osteoid and callus gain an impetus to grow when they contact and creep along the surfaces of well tolerated fragments, while no such acceleration or growth occurs along the surfaces of purely inert metal plates. An historical review of the fate of autogenous and homogenous bone grafts is presented by Chase & Herndon (16). This is an excellent source for those interested in background material regarding the use of bone grafts. As the authors state, it might help to avoid duplication of effort, since many of the problems now studied seem to have been studied previously. The authors feel that one of the greatest problems yet to be solved is that of the specific factor in bone which produces the difference of behavior between homogenous and autogenous bone.

Healing of Bone

The failure of a surplus of minerals in the diet to accelerate the healing of experimental fractures is noted by Key & Odell (17). The authors state that they had hoped first to obtain proof that mineral mixtures accelerate the healing of fractures, and then to search for the combination of elements responsible for the beneficial results. They stated that, unfortunately, their hopes had not been realized, and in their experimental animals they had not been able to detect any significant difference in the rate or manner of fracture healing between the mineral-fed animals and the control animals. The studies were made in Deaf Smith County, an area in which the water contains a relatively large amount of fluorine.

Fracture Treatment with Intramedullary Nails

The above discussions about bone grafts and bone healing lead to a discussion of fractures. Fracture treatment these days has been considerably

altered in many instances by the use of intramedullary nails. Those used at present, for the most part in long bone fractures, are as follows: The cloverleaf, the Rush with the round hook on the end sledrunner point, and the Hanson-Street diamond-shaped nail are used in the femur. The Lottes nail (18) and the Rush nail are used in the tibia. There are many other uses of the Rush nail (19). Key (20) attempts to evaluate the proper use and to illustrate and enumerate the uses of medullary nailing of fractures of long bones.

Of particular interest is the insertion of the intramedullary nail through the femur and into the tibia as a means of accelerating knee fusion in cases in which this is required. Murray (21) of Syracuse has been doing this for the last several years and has had success with all five cases attempted. He states he obtains more rapid fusion, and that the patients are permitted up and about without a brace, using only crutches immediately postoperatively as soon as the general postoperative effects have been overcome. More rapid fusion of the knee joint inconveniences the patient a much shorter time, thereby leading to a resumption of normal life more rapidly.

Replacement Prostheses

In October, 1954, the American Academy of Orthopedic Surgeons published a survey on femoral head replacement prostheses (22) in which 31 types are noted. The one most frequently used was the Thompson prosthesis, and the second, the Moore. The Judet prosthesis and 20 other prostheses, variations of different types, are listed. Complications of the use and abuse of prostheses are listed, including the protrusion of the stem from the shaft, dislocation of the prosthesis, fracture of the femur, broken prosthesis, pain, infection, calcification, instability, etc. It is interesting to note the indications suggested for the use of prostheses. The majority were for nonunion of a fracture, arthritis, aseptic necrosis of the femoral head, fresh fractures, and fresh fractures in the aged. It is of considerable importance, I think, that this survey came as a result of the reports of 744 members of the Academy of Orthopedic Surgeons. It appears in general that more orthopedic surgeons are using the prosthesis than had been reported previously. The technique seems to be better, the indications are more strict, and the present types of prostheses have narrowed down to a metallic version of the Judet or the use of the intramedullary type.

At the present time, the femoral head replacements for the most part are applied with an intramedullary element. This has prompted a great number of articles suggesting primary use of the prosthesis for fracture of the femoral neck (23). Peterson (24) feels that the procedure should be carried out as an initial operation for elderly patients with femoral neck fractures, and should be performed within 48 hours after the injury. Thompson (25) has also discussed the use of vitallium intramedullary hip prostheses, and developed one of his own. The problem of the broken Judet prosthesis is discussed by Pridie (26). Levy *et al.* (27) have also discussed the complication of the Judet arthroplasty, which is attributable to foreign body reaction

when using a nylon prosthesis, and conclude "it is felt advisable to refrain from using nylon Judet heads for replacement arthroplasty."

Material failures in hip prostheses are discussed by Heck & Chandler (28), who state that 10 cases of failure of materials had been observed in hip prosthesis. Acrylate and nylon do not appear to have all the qualities necessary to make their use wholly justified for hip surgery at this time. Experimental work was carried out to clarify the problem, and the findings presented show the need of a thorough study. Nine of the ten patients were treated secondarily with a metal intramedullary type of prosthesis, and one was treated by arthrodesis of the hip. There have been some reports, too, of some failures of metal prostheses when inferior grades of metal were used. This has been seen in certain types of stainless steel. Replacement of the humeral head has been found to be of possible value in selected cases (29).

Fractures—General Treatment

The Colles fracture still presents a problem, and this common type of fracture is discussed at almost every medical meeting at which treatment of fractures is considered. Someone always has a new method of treatment, while others re-emphasize the older methods. One of the methods reviewed as a representation of an old method is described by Strong (30), who recommends the Watson-Jones method for the treatment of Colles fractures, with traction on the thumb and index finger and counter-traction at the elbow. He suggests it would be well to use hyaluronidase locally in the fracture site, if treatment of the reduction has been delayed until several days after the injury. He prefers a posterior molded plaster splint which extends around the radial and ulnar surface of the wrist and forearm, but which does not meet on the volar surface; apparently, full extension of the elbow is obtained by this means.

The complications and the dangers of supracondylar fractures of the humerus are emphasized once again (31). The importance of early recognition of vascular and neural complications is noted, as is the need for early treatment in order to prevent Volkmann's ischemic contracture, etc. Madsen (32) also discusses supracondylar humeral fractures, and he offers some variation of the method for reducing such fractures by using lateral rotation of the arm combined with mechanical traction, manipulation, and fixation in a plaster shoulder spica.

The management of navicular fractures is discussed by Stewart (33). He states that accurate reduction and adequate continuous immobilization are required for solid bony union after carpal-navicular fractures. He urges the use of a cast incorporating the base of the thumb up to the interphalangeal joint, and advises that the plaster should be removed every 4 to 6 weeks with x-ray examination to determine progress of healing, but the patient should not move the thumb while the cast is off. Some old fractures may require immobilization for more than 21 weeks, as compared with 12 weeks

for fresh injury cases. The experience of the author in this instance has been that some fractures of the carpal scaphoid may require immobilization for as long as 52 weeks or even 78 weeks.

Severe fractures of the ankle are described by Coonrad and Bugg, (34), who advocate early open reduction of such fractures when severe injury to the ligaments and disruption of the ankle mortise occur They have stated that failures to obtain good results in these are attributable to (a) a common tendency to be satisfied with a fairly normal reduction; (b) not forewarning the patient that more than one manipulation under anesthesia may be necessary; (c) failure to obtain x-rays in the true antero-posterior and lateral projections; (d) not overcoming soft tissues trapped between the fragments. Where reduction is not obtained by closed manipulation, surgical operation should be carried out before bleb formation which complicates the issue and may result in infection. Thus, early open reduction is suggested.

An excellent review of the situation as regards fractures, particularly in children, is compiled in the book "Fractures in Children" (35) which should be available in all hospital libraries.

Deformities

Brockway, Craig & Cockrell (36) presented a study of the end results of 62 stapling operations. Seven patients were stapled for knock-knee deformity and 42 for limb-length discrepancy. Partial extrusion of staples was fairly common. In each of 16 patients they carried out an epiphyseal arrest after the staples had been removed, because of the continued major discrepancy in leg lengths. Burying of staples was common, especially when these had been placed under the periosteum. Back-knee deformities as a postoperative complication were too frequent. It was suggested that the staples should be placed more posteriorly in the tibia. The results in patients with knock-knee deformity were best, and yet in two patients a significant back-knee deformity developed.

Blount, who introduced the stapling operation for such deformities, discussed this paper. He re-emphasized the proper placing of the staples, checking by antero-posterior and lateral x-rays at the time of the surgery. He also emphasized the fact that the staples should be placed through the periosteum, not under it, and he felt that the repeated removal of the staples, rather than insertion, caused injury to the epiphyseal cartilage. He has found that four years of stapling during a period of rapid growth will not cause permanent arrest, that in the first few weeks after removal of the staples the epiphyseal plate suddenly expands to almost twice its normal width, and the growth of the epiphysis is temporarily accelerated. He advises against the use of staples in children less than eight years of age.

Epiphyseal stapling for leg deformities is discussed by Dalton & Carpenter (37). Epiphyseal stapling, a surgical procedure, could be carried out to

correct deformities at a later stage than that in which correction is possible by the use of bracing and exercise. In the author's hands, and the hands of his associates, this procedure has proved to be of considerable benefit.

Bunnell (38) describes surgery of the arthritic hand. This is a rather interesting though technical paper, intended primarily for the hand surgeon and for the orthopedic surgeon. It is noted here so that it will call to the attention of internists, interested primarily in arthritis and similar generalized diseases, the possibility of some improvement by means of surgery in some of the severe deformities that occur in arthritic hands and feet.

Drug Therapy in Diseases of the Bones and Joints

The newer modifications of cortisone are still holding the greatest interest as a means of treatment of arthritis in particular, and as adjuncts in the treatment of the affections of the bones and joints. The use of hydrocortisone injected into the shoulder joint and other joints, particularly the knee joint, in the osteoarthritic as well as the rheumatoid arthritic seems to have been of value, and in its use personally by the author it has proved to be of considerable benefit. In our office we have been using hydrocortisone for approximately 30 months, in doses of 12.5 mg. to 25 mg. directly into the joints, with success in the majority of cases. The prolonged use of large amounts of cortisone was followed by vertebral demineralization and pathological fractures (39), including four instances in males.

Among the medications which are particularly useful in joint diseases and in injuries in the region of bones and joints is hyaluronidase, very useful in hemarthrosis, hematoma, and edema of traumatic origin. The recommended dose is about 1500 units of the powdered enzyme dissolved in 3 to 5 cc. of one per cent procaine. It is important to prevent impending Volkmann's ischemic contracture without a surgical procedure and to overcome the extravasation of blood into joints in hemophilia, as well as into any confined soft tissue space such as hand space, hematomata, etc. (40).

The use of the antibiotics has been changing considerably in the past year, not only because of the appearance of newer antibiotics but also because there has been a trend away from the use of penicillin in many areas, since a considerable number of patients have been found to be sensitive to penicillin. In instances in which it would appear that the penicillin sensitivity of the organism was greater than, or at least equal to, that of some newer antibiotic, the newer antibiotic has been used. Penicillin with tripelennamine (Pyribenzamine hydrochloride), known as penicillin PBZ, was administered by Matlin (41). He used 500 doses of 200,000 units of penicillin with 50 mg. of tripelennamine in both adults and children, of whom all but seven had received penicillin in some form before; some of these already had a history of sensitivity, and some had a history of allergy to other medications, or to food or clothing. Only one of four adults with a history of sensitivity to penicillin had any reaction, and this was handled by the use of

additional tripelennamine afterward. Thus, only one individual showed any sensitivity with penicillin PBZ, and this was not a dangerous sensitivity.

Rehabilitation

The topic of rehabilitation is prominent in the presently popular aspects of medicine. This seems logical in these days of increasing use of machinery and automation. Less physical labor than before is required of a person in order that he be employable, and he is more readily transported to the site of industry. Many patients now salvaged would have been shelved in earlier times and would have required care at home by their families and friends.

Kessler (42) describes quite completely what should be done to effect the most complete return of working capacity to patients disabled by amputation, arthritis, paraplegia, poliomyelitis, etc. The integrated efforts of many special services, including non-medical ones, are essential. These include those of the orthopedic surgeon, neurosurgeon, physiatrist, psychiatrist, internist, and pediatrician; physical restoration, vocational guidance, and training and placement of the handicapped are involved. It is of great importance to introduce the physical therapist to the patient at the earliest possible moment.

The social and economic aspects of rehabilitation of older patients have been reviewed (43, 44). Unless the hospital staff is alert to the possibilities of rehabilitation, the older disabled patient may remain too long away from his home and may become neurasthenic, dependent, and demanding. It is urged that all physicians should have the proper concept of rehabilitation, and that the latter should not be withheld from patients more than 45 years of age as it was in many instances in the past.

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APPLIED PREVENTIVE MEDICINE[1]

(Rheumatic Fever and Rheumatic Heart Disease)

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Preventive medicine is an approach to the patient, an awareness of his broad needs, and an anticipatory attitude on the physician's part. It is these things rather than merely a series of specific techniques to be applied to ward off disease. If we use the word "preventive" in its Elizabethan meaning, the idea of "coming before" (prae-venire) is clear. This concept of forestalling disease when possible, as well as avoiding complications and sequelae, needs emphasis. Smith & Evans (1) have said that the core of preventive medicine is "the adjustment of the individual patient to his physiological equipment and status," which expresses the major concept quite well.

Much data could be collected on recent techniques in preventive medicine. This would be less valuable, however, than illustrating certain concepts resulting from a number of recent discussions of the subject that help to clarify the basic idea. There is much confusion about preventive medicine in the literature. Some basic misconceptions have muddied the water considerably and even kept preventive medicine from finding its rightful place in medical education.

The term "preventive medicine" is often confused with "social medicine" and with "public health," as well as with other terms. It is well to reserve the use of "public health" for the aspects of health work carried on as organized community action. Public health is thus one aspect of preventive medicine, though not synonymous with the broader, more inclusive term.

Use of the term "social medicine" causes more of a problem in the United States than it does in Canada or the United Kingdom. In the latter countries it by no means implies "socialized medicine," though it is concerned among other things with studying the advantages and disadvantages of different degrees of socialization under varying circumstances. This is simply one aspect of medicine in relationship to man and his fellow men. The latter concept is perhaps the most important one embodied in the idea of social medicine.

When medicine is practiced in accordance with the best knowledge available at a given time, such practice is bound to include a great deal more than palliative treatment of such disease as may be identified. The best medical practice, and this is preventive medicine, makes a much broader approach. It must also include efforts to (*a*) promote health, (*b*) provide specific protection (when this is available), (*c*) make early diagnosis and institute prompt treatment of such diseases and disorders as are discoverable with modern diagnostic measures, (*d*) make efforts to limit any disability which may ap-

[1] The survey of literature pertaining to this review was completed in July, 1955.

pear, and (*e*) develop and execute such timely rehabilitative procedures as may be appropriate. These five aspects of preventive medicine may be called "levels of prevention" (2), and activity at one or more of these levels is appropriate as a given disease or disorder passes successively through the stages characteristic of its own natural history.

The importance of acquiring more exact knowledge of its natural history is emphasized for us when we plan our attack on the disease. We can concentrate our efforts at the most strategic points, or levels of prevention, when we have full information about the stages through which the natural history passes, from before the time demonstrable disease exists to the end point at which recovery or death of the patient or stabilization or latency of the disease process takes place.

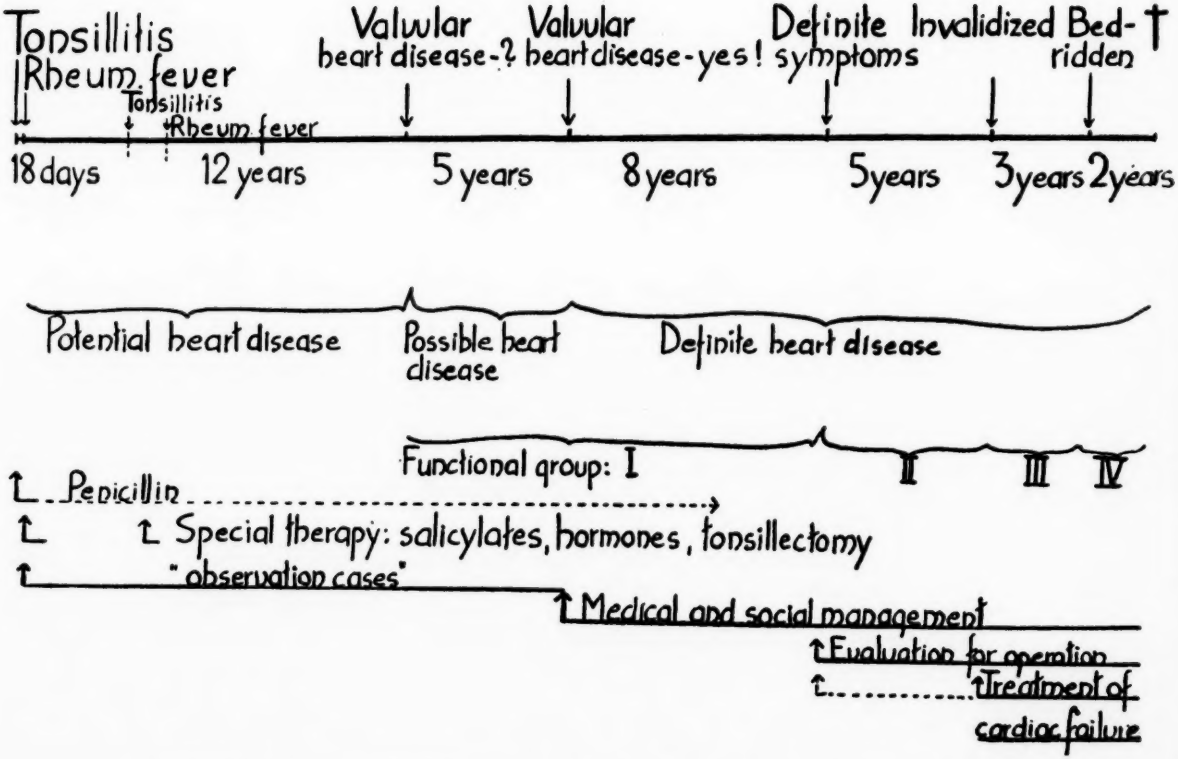
If we consider the problem of rheumatic fever as an example, it may clarify the foregoing statements. Biörck (3) presents a very interesting chart (reproduced below), summarizing on the top line the natural history of rheumatic heart disease from the first attack of tonsillitis to death. His diagram does not refer to the interaction of the human host, the disease agent (the streptococcus as at least a major offender in this case), and the environment in which the patient lived. All three of these—the host, agent, and the environment—were presumably in some sort of equilibrium before the manifest phases of the natural history appeared. Thus the multiple factors in disease causation find emphasis. The lower portion of Biörck's diagram shows strategic action taken at different levels of prevention. Using basically the same idea as Biörck does, let us elaborate and broaden the concept somewhat.

Definition of the Disease

A study of the natural history of a disease process as it occurs in the total population, and not merely in hospital work or private practice, is a complex problem. Yet without such study in the community as a whole, we can have only an incomplete picture of the course a disease follows, and of the various manifestations it may have from the mildest type of disorder on the one hand, to death on the other. This variation in degree has been described as the "biologic gradient" of disease [Gordon (4)], and it is most important in broadening our understanding of natural history to search out cases of varying gradations of severity so that we may have the total picture. Dorn (5) says on this point that "growing emphasis upon prevention and early detection tends to push the stage at which a pathologic process is called a specific disease increasingly closer to the beginning of the process."

This type of study, essentially epidemiologic, must use biometric methods. Men like Bradford Hill of England, Lowell Reed, and many others in the United States have pointed out an important deficiency in our medical education that is now being remedied in many schools (6). Dorn says:

> Almost every phase of the practice of medicine necessitates at least the rudimentary application of statistical ideas. . . . Nevertheless medicine, among the disciplines in which enumeration and measurement are commonly employed, has been the least



Reprinted after Biörck (3) with the kind permission of the author and the publisher, C. V. Mosby Co.

influenced by the developments in statistical theory and techniques of the past two decades. . . . When we turn from the subject of clinical trials to that of investigations of the etiology of disease we find the basic concepts of biometry and epidemiology still largely unrecognized. . . . That this is so should not be surprising since it reflects the training of the physician in the interpretation of individual case histories. . . .

The first step in the application of biometric methods is an unequivocal definition of the events to be counted or measured.

The problem of defining precisely what is meant by rheumatic fever is very difficult. We have no specific serological test as is the case with syphilis, and no specific bacterium is as yet identifiable as is true of tuberculosis and numerous other diseases.

The concept of rheumatic fever as a specific disease entity is a relatively new one. Paul (7) traces the historical development of the concept in a fascinating story. He recalls how the arthritic aspects were confused among the great mass of disease conditions in which involvement of the joints occurs, and how in the early nineteenth century the importance of cardiac involvement became recognized. When in 1904 Aschoff discovered what he believed to be specific pathologic lesions, the concept of the "individuality" of rheumatic fever advanced considerably. Jones (8) clarified the clinical picture by proposing criteria which might serve to restrict the diagnosis to those cases definite enough to provide a basis for comparative evaluation of various methods of care.

The association of rheumatic fever and tonsillitis was observed in 1886, and since about 1930 the importance of group A hemolytic streptococci as a factor in etiology has met increasing acceptance. In fact, the question now is, whether or not rheumatic fever is simply one of a large group of manifestations of streptococcicosis, and not a specific separate disease entity.

The Natural History of Rheumatic Fever

A statement of the natural history of a disease differs from many classical textbook pictures in certain important respects, though it would be useful if authors of texts made more conscious efforts to define the natural history of the disease entity with which they were dealing.

Natural history is concerned with careful description of the dynamic, on-going interaction which takes place over a period of time among the human host, the agent (microbiologic or otherwise) which may be involved, and the environment in all its aspects. It emphasizes the disease process as it occurs in "nature" not influenced by man's intervention, though the effects of man's control efforts must also be evaluated. The aid of both natural and social sciences is enlisted in seeking to throw light on what is taking place.

In considering the natural history of rheumatic fever, it will be useful to discuss the host, the agent, the environment, and the interaction among all three which results in the clinical disease picture.

The Human Host

Rheumatic fever is primarily a disease of childhood, with the time of onset reaching an average peak between 5 and 15 years of age. No sex predisposition is apparent, though girls tend to have chorea more often than do boys. Racial factors seem unimportant, though certain racial groups, such as Irish and Italians in mixed populations like that of the United States, may tend to live under environmental conditions that favor the disease. No special physical characteristics are of demonstrated importance, though "poor health in childhood for which there is no obvious explanation is the usual picture (9)." The high familial incidence is striking, and after reviewing the situation Paul concludes, "there is evidence to suggest that the *tendency* to acquire rheumatic fever is inherited."

Individuals who develop the disease show "marked non-specific hyperirritability to many stimuli," according to Bland & Jones (9) who noted that although attacks are usually precipitated by streptococcal infection, it is not uncommon for them to be "triggered off" by "trauma, surgical operations, exposure to cold," etc. In fact, there is much evidence to suggest that the person with rheumatic fever has some sort of allergic reaction which leads to excessive antibody production in some respects comparable to the Arthus or Shwartzman phenomena. Most observers accept the idea that there must be a latent period between the first streptococcal infection and the first bout of rheumatic fever, during which time an altered reaction capacity develops.

The Agent

If the group A hemolytic streptococcus is not the "etiologic" agent in rheumatic fever, it certainly is of very great importance in the natural history. Both the original attack of rheumatic fever and the recrudescences, recurrences, or exacerbations so characteristic of the disease ordinarily follow upper respiratory streptococcal infections. No one type of streptococcus is regularly involved, but there seems to be a relationship between what some workers call "rheumatogenic strains" (10), independent of type, and their power to elaborate erythrogenic toxins capable of producing scarlet fever in the host whose susceptibility is such that he reacts in this manner.

There is a definite seasonal relationship between peaks of streptococcal infections and of rheumatic fever incidence, both being at their height in the cold, damp months.

There is very good documentation of the effects of antibiotics (provided the prevailing streptococci are not resistant) in treating the streptococcal infection so that rheumatic fever does not subsequently occur, and in prophylaxis of streptococcal infections thereafter (11).

The Environment

The association between cold, damp climate and clinically recognized rheumatic fever is evident, but it is now well known that the disease not only

occurs in warm places, but that it may even reach epidemic proportions there. Whether the dampness and cold is itself responsible, or whether it simply leads to overcrowding indoors with greater opportunities for cross-infection, is not known.

For a long time it has been realized that rheumatic fever is particularly common among the needy population of large cities, but whether the association here results from overcrowding, undernutrition, or "unhygienic surroundings" has not been established.

It is undoubtedly true that when large numbers of susceptible recruits are crowded together in war-time, streptococcal infections and rheumatic fever occur, both often assuming epidemic character. Paul (7) says, "Its occurrence is most frequent among people who are herded together within doors during periods of inclement weather." It is definitely a "crowd" disease.

The Interaction

When a group of susceptible hosts, under appropriate environmental conditions, is attacked by streptococci of the proper type and strain, a portion of them develop rheumatic fever. What this proportion may be is not known precisely, since so many variables are involved, such as the age and susceptibility (not readily if at all determinable, as with the Schick test in the case of diphtheria) of the population. In military populations, $\frac{2}{3}$ per cent of those with streptococcal infection develop rheumatic fever [Rammelkamp *et al.* (12)], apparently without regard to the severity of the preceding streptococcus infection.

In the United States Navy studies of World War II, Coburn & Young (10) used the following nomenclature for classifying streptococcal disease:

Primary infections
"catarrhal fever," tonsillitis, pharyngitis, scarlet fever, tracheitis, laryngitis, tracheobronchitis, bronchitis, pneumonia, lymphangitis, erysipelas, cellulitis.

Septic complications
Lymphadenitis, otitis media, sinusitis, mastoiditis, meningitis, empyema, peritonitis, endocarditis.

Sterile sequelae
Rheumatic fever, acute nephritis, erythema nodosum.

This large category of the effects of streptococcal disease illustrates the need for searching for other manifestations as well when rheumatic fever is present.

Jones (8) divides the manifestations of rheumatic fever into major and minor groups, and Bland & Jones (9) in a very careful 20 year follow-up of 1,000 cases note the percentage of those showing certain manifestations:

Major manifestations:

Carditis	"The most common and the most serious and unequivocal manifestation." On recovery from the initial illness, 65% had signs of rheumatic heart disease.

Arthralgia and Arthritis	41% 40%	
Chorea	51%	Commoner among females and younger patients.
Subcutaneous nodules	10%	Largely limited to earlier decades.
Minor manifestations:		
Fever		
Precordial pain	24%	
Abdominal pain	11%	
Epistaxis	27%	of children
Rashes	8%	
Laboratory findings		Hemoglobin, white blood count, sedimentation rate, x-ray of heart, electrocardiagram and antistreptolysin titer.

The recurrences so characteristic of rheumatic fever are usually precipitated by streptococcal infections. "The degree of disability and the ultimate longevity of those with injured hearts are largely determined by the frequency, duration, and severity of the recurrences (9)." In the Bland-Jones series, one-fifth had recurrences during the first five years of follow-up; one-tenth during the second five years; and one-twentieth in the third five-year period. Recurrences were rare thereafter.

TABLE I

SUMMARY OF TWENTY YEARS' OBSERVATION
1000 PATIENTS 1921–1951

	Potential Rheumatic Heart Disease	Rheumatic Heart Disease	Dead
Original status (average age—8 years)	347	653	
Ten years later (average age—18)	323	475	202
Twenty years later (average age—28)	319 (3 lost)	380 (2 lost)	301

Table I (from the Bland-Jones study) is very illuminating. Of the 301 deaths in the series, 80 per cent were attributable to rheumatic fever or congestive failure or both, and 10 per cent to bacterial endocarditis. Either anatomical damage to the heart valves or extra work for the heart or both predispose to bacterial endocarditis, which is usually because of *Streptococcus viridans*, and which not infrequently follows dental manipulations.

Cardiac surgery has now been developed to the point where a stenotic mitral valve can be widened successfully with quite low operative mortality (13).

Having summarized certain points in the natural history of rheumatic fever, we show in Table II how preventive measures may be applied to the host, agent, or environment at the various levels of prevention. This table

TABLE II

PREVENTIVE MEASURES IN RHEUMATIC FEVER APPLICABLE AT DIFFERENT LEVELS OF PREVENTION BASED ON THE NATURAL HISTORY OF THE DISEASE

Level of Prevention	Applied to Host	Applied to Agent	Applied to Environment
1. Promotion of health	Take account of heredity factor. Maintain good nutrition.		Provide proper housing. Provide emotional and financial security.
2. Specific protection	Tonsillectomy if indicated	Treat streptococcal infection with penicillin to avoid original rheumatic fever, if possible. Maintain penicillin prophylaxis over prolonged period if rheumatic fever occurs. Special attention during subsequent streptococcal infections; after trauma; before dental manipulation, or operation.	Protect from exposure to streptococci; avoid over crowding. Provide separate bed and space for isolation of patient. Extra care during cold, damp months.
3. Early diagnosis and prompt treatment.	Concentrate case finding on children. Salicylates, hormones?* Rest until active process subsides.	Vigorous penicillin therapy while throat culture remains positive.	Hospitalization in acute phase. Management of social factors (medical social worker?).
	(Recrudescences must be watched for carefully and treated promptly, especially during first ten years after original attack of rheumatic fever.)		
4. Disability limitation	Treatment of cardiac failure or arrhythmia as they develop. Evaluation for cardiac surgery if indicated. Check for evidence of bacterial endocarditis.	Continue penicillin. Antibiotic therapy suited to infecting organism for bacterial endocarditis.	Adjustment of family and patient to long-term illness. Convalescent home? Keep education up to normal if possible, using home teacher. Suitable housing, if heart damage requires.
5. Rehabilitation	Cardiac surgery if indicated. Physical activity up to cardiac capacity; avoid making "cardiac cripples" unnecessarily.	Continue penicillin.	Education up to mental capacity. Vocational guidance as required. Attention to mental health and emotional support.

* Carefully controlled experiments in both the United States and the United Kingdom failed to demonstrate any superiority of either ACTH or cortisone over aspirin. The follow-up continues (14).

has 15 "boxes," and if enough is known about the natural history of a disease, some preventive measure may be included in each of the "boxes." This technique is applicable to any disease. Rheumatic fever, as was pointed out earlier, is used simply as an example here.

One important value of this type of diagram is that it reveals gaps in available preventive measures, due in some cases to lack of complete knowledge of natural history.

A rheumatic fever control program for an individual patient with sufficient financial means to provide whatever is necessary is complicated enough. But when the disease strikes those in poor economic circumstances, as is so often the case, community facilities must be available to meet the needs. And when community action is called into play, the program becomes a public health one, regardless of whether a voluntary agency such as a heart association, or an official agency, such as the health department, is concerned (15). The practitioner who wants to practice preventive medicine in the broad sense of the term must be as familiar with what his community agencies have to offer his patients as he is with the pharmacopeia. This is even more true with long-term illness such as rheumatic fever than with self-limited acute disease.

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ANNOTATED LIST OF REVIEWS IN MEDICINE

By Eaton M. MacKay and Lois L. MacKay[1]
Beverly Hills, California

This list of reviews now comes into its seventh year. Heretofore the listing has more or less followed the subject headings of the *Annual Review of Medicine*. Such a classification has not been an easy one in which to properly place many articles, so we have begun to change our subject classifications toward a more systematic arrangement. For the moment this makes for a somewhat incongruous mixture of organs, functions, and clinical fields as equal compartments. No classification is ever ideal, but in the next volume we hope to make the various divisions in which the reviews are placed still more usable. Also, through a new plan, we expect to attain an even more complete coverage of the literature as well as greater selectivity, which the rapidly increasing number of reviews makes necessary. Lastly, in addition to our irregular annotations, each review will be coded for certain qualities in a systematic manner.

The following includes reviews published after those which formed our list in Volume 6 of the *Annual Review of Medicine* and prior to December, 1955. It will be noted that more reviews in foreign languages are listed than in the past. This is because of an increase in the number of reviews which are being published in countries which use a language other than English, as well as improvement in their quality. The nature of the subject matter of the foreign reviews should be obvious from our annotations.

Allergy

1. "Miscellaneous Review of Allergy 1954," Halpin, L. J., *Ann. Allergy*, **13**, 326–68 (1955), 167 references. A good review of the literature.

2. "Allergie," Bigliardi, P., *Dermatologica*, **110**, 456–62 (1955), 39 references. A good review of recent literature.

3. "Pediatric Allergy," Collins-Williams, C., and Ratner, B., *Ann. Allergy*, **13**, 196 (1955), 97 references. A critical review of the literature for late 1953 and most of 1954.

4. "Symposium: Ocular Allergy," Theodore, F. H., *et al.*, *Trans. Am. Acad. Ophthalmol. Otolaryngol.*, **59**, 490–500 (1955), 16 references. An outline of the differential diagnosis of external eye diseases on an allergic basis.

5. "Allergy of the Eye, Ear, Nose and Throat," MacQuiddy, E. L., and Sheldon, J. M., *Arch. Ophthalmol.*, **59**, 749–62 (1954), 94 references. A review of the literature for 1950, 1951 and 1952.

6. "The Role of the Psyche in Allergic Disease," Burden, S. S., *Ann. Internal Med.*, **43**, 1283–1301 (1955), 14 references. A survey of its present status.

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7. "Hay Fever," Kaplan, M. A., Ehrlich, N. J., and Aaronson, A. L., *Ann. Allergy*, **13**, 594–626 (1955), 292 references. A review of the literature of 1953–54.

8. "Bronchial Asthma," Alexander, H. L., *Disease-a-Month*, 3–32 (March, 1955), 18 references. A good review of theory and practice in the current control of this ailment.

9. "Bronchial Asthma," Gottlieb, P. M., *Ann. Allergy*, **13**, 423–505 (1955), 381 references. A review of the literature of 1954.

10. "Entzündung Entzündungsbereitschaft und Immunität," Schwartz, P., *Acta Neurovegetat.*, Suppl. **3**, 4–142 (1955), 233 references. A morphological-pathogenetic study which includes a thorough review of the recent literature.

11. "Immunization," Edsall, G., *Ann. Rev. Microbiol.*, **9**, 347–68 (1955), 121 references.

Anesthesia

12. "Anesthesia: Fifty Years of Progress," Beecher, H. K., and Ford, C., *Intern. Abstr. Surg.*, **101**, 105–39 (1955), 273 references. An excellent survey of a specialty which has made great advances during this period.

13. "General Anesthesia and Respiration," Dripps, R. D., and Severinghaus, J. W., *Physiol. Revs.*, **35**, 741–77 (1955), 248 references. A review purposely limited to the effects of general anesthetic agents and accompanying surgical procedures on the central and reflex control of respiration.

14. "L'anesthésie en oto-rhino-laryngologie," Guns, P., and de Temmermàn, P., *Acta Oto-Rhin.-Laryngol. Belg.*, **9**, 101–235 (1955), 221 references. A comprehensive report made to the Belgian specialty society.

15. "Anaesthesia for Cardiac Surgery," Brown, A. I. P., and Sellick, B. A., *Brit. Med. Bull.*, **11**, 174–77 (1955), 3 references. A review of the subject.

16. "Renal Function during General Anesthesia," Papper, E. M., *Bull. N. Y. Acad. Med.*, **31**, 446–52 (1955), 22 references. A short survey of the literature.

17. "Evaluation of Pentothal Anesthesia after Twenty Years—Its Use and Abuse," Collins, J., *Bull. N. Y. Acad. Med.*, **31**, 438–45 (1955), 16 references. A brief critical review of the subject.

18. "Hypothermia," Delorme, E. J., *Brit. Med. Bull.*, **11**, 220–25 (1955), 39 references. A very short summary of the subject.

19. "Practical Applications of Hypothermia," Ross, D. N., *Brit. Med. Bull.*, **11**, 226–28 (1955), 7 references.

Bones, Joints, and Muscles

Physiology.

20. "Dynamic Anthropometry," Count, E. W., *et al.*, *Ann. N. Y. Acad. Sci.*, **63**, 435–636 (1955), 314 references. A symposium of 16 papers by 16 authors on divergent aspects of the subject.

21. "Elementary Processes in Muscle Action: An Examination of Current Concepts," Morales, M. F., Botts, J., Blum, J. J., and Hill, T. L., *Physiol Revs.*, **35,** 475–505 (1955), 216 references. A careful review of the better understanding of muscle action which has come with the contributions of recent years.

22. "Models for the Study of the Contraction of Muscle and of Cell Protoplasm," Hasselbach, W., and Weber, A., *Pharmacol. Revs.*, **7,** 97–117 (1955), 125 references.

23. "Structural and Functional Aspects of Myosin," Szent-Györgyi, A. G., *Advances in Enzymol.*, **16,** 313–60 (1955), 246 references. For the biochemist.

24. "The Physiology of Connective Tissue," Baker, B. L., and Abrams, G. D., *Am. Rev. Physiol.*, **17,** 61–78 (1955), 211 references.

25. "Metabolism of the Mucopolysaccharides of Connective Tissue," Dorfman, A., *Pharmacol. Revs.*, **7,** 1–31 (1955), 159 references. An unusually fine review of a currently lively field of possible interest to innumerable investigators.

26. "Metabolism and Clinical Significance of the Carbohydrate Components of Connective Tissue," Calkins, E., Soodak, M., and Bauer, W., *New Engl. J. Med.*, **253,** 865–72 (1955), 85 references. A brief survey of recent contributions.

27. "Inhibition of Hyaluronidase," Mathews, M. B., and Dorfman, A., *Physiol. Revs.*, **35,** 381–402 (1955), 154 references. A critical review of some of the recent studies.

Diseases.

28. "The Human Skeleton in Forensic Medicine, Part I," Krogman' W. M., *Postgrad. Med.*, **17,** No. 2, A48–A62; No. 3, A34–A46 (1955), 16 references. A detailed summary of age, sex, and race data on the human skeleton.

29. "Nonrachitic or Physiologic Bowing," Christie, A., and Stempfel, R. S., *Postgrad. Med.*, **17,** 306–12 (1955), no references. A well done short pictorial "scientific exhibit" outline.

30. "Fractures of the Extremities in the Newborn," Madsen, E. T., *Acta Obstet. Gynecol. Scand.*, **34,** 41–74 (1955), 61 references. An analysis of 786 fractures among 105,000 newborn infants.

31. "Coxa Vara Infantum," Magnusson, R., *Acta Orthopaed. Scand.*, **23,** 284–308 (1954), 24 references. An analysis of 67 cases.

32. "Spondylolisthesis, its Cause and Effect," Newman, P. H., *Ann. Roy. Coll. Surgeons Engl.*, **16,** 305–23 (1955), 14 references. A useful well illustrated clinical summary of the subject.

33. "Cervical Disk, Shoulder-Arm-Hand Syndrome," Craid, W. McK., and Witt, J. A., *Postgrad. Med.*, **17,** 267–79 (1955), 9 references. A well illustrated outline review of the subject.

34. "Disc Lesions, Fact and Fallacy," Crisp, E. J., *Guy's Hosp. Gaz.*,

69, 475–81 (1955), no references. Another worker reviews his notions on the subject.

35. "Slipped Discs and All That," Stamm, T. T., *Guy's Hosp. Gaz.*, **69,** 260–64 (1955), no references. The author's views are well put together, and they are good ones.

36. "The Munkfors Investigation," Hult, L., *Acta Orthopaed. Scand.*, Suppl. 16, 5–76 (1954), 66 references. A study of the frequency and causes of the stiff neck-brachialgia and lumbago-sciatica syndromes in a large group of males under 50 years of age.

37. "Cervical, Dorsal and Lumbar Spinal Syndromes," Hult, L., *Acta Orthopaed. Scand.*, Suppl. 17, 5–102 (1954), 56 references. An historical survey and a study designed to determine their relation to the special strains imposed by heavy work.

38. "Experiences in Surgical Treatment of Lumbar Disk Herniation," Svaar, O., *Acta Chir. Scand.*, **109,** 97–105 (1955), 12 references. A critical review of the author's personal experience with 157 cases.

39. "Osteopetrosis in Adults," Hinkel, C. I., and Beiler, D. D., *Am. J. Roentgenol. Radium Therapy Nuclear Med.*, **74,** 46–64 (1955), 62 references. A well illustrated review of the clinical and roentgenological findings in this disease.

40. "Osteitis Condensans Ilii," Wassmann, K., *Acta Med. Scand.*, **151,** 151–54 (1955), 12 references. A short review of this radiological abnormality of doubtful clinical importance.

41. "The Hip Joint—Surgical Approaches and Procedures," Capener, N., *Ann. Roy. Coll. Surgeons Engl.*, **17,** 28–47 (1955), 25 references. A profusely illustrated working review.

42. "The Shelf Operation," Jakobsson, A., *Acta Orthopaed. Scand.*, Suppl. 15, 5–120 (1954), 103 references. A survey of the literature and analysis of a series evaluating the results in congenital dysplasia, subluxation, and dislocation of the hip joint.

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45. "The Results of Tendon Suture of the Hand," Hange, M. F., *Acta Orthopaed. Scand.*, **24,** 258–70 (1955), 12 references. A review of the results obtained in a series of 500 patients.

46. "Fifty Years' Progress in Surgery of the Hand," Mason, M. L., *Intern. Abstr. Surg.*, **101,** 541–64 (1955), 401 references. A considered critical review of the subject based on an extensive literature.

47. "Aetiology and Pathogenesis of Rheumatoid Arthritis," Dresner, E.,

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48. "Rheumatoid Arthritis," Ragan, C., and Snyder, A. I., *Disease-a-Month*, 3–51 (November, 1955), 35 references. A critical clinical review of a subject about which much is written but little is known.

49. "A Review of Myodysneuria (Fibrositis)," Gutstein, R. R., *Am. Practioner and Dig. Treatment*, **6,** 570–77 (1955), 42 references. A short review of its role in vasomotor disorders and functional gastro-intestinal diseases.

50. "Zur Genetik der Myopathien," Becker, P. E., *Deut. Z. Nervenheilk.*, **173,** 482–98 (1955), 46 references. A review of recent literature on the genetics of the myopathies.

51. "Zur Klinik der Myopathien," Becker, H., *Deut. Z. Nervenheilk.*, **173,** 454–81 (1955), 168 references. A review of the clinical literature on the myopathies.

52. "Symposium on Myasthenia Gravis," Gammon, G. D., *et al.*, *Am. J. Med.*, **19,** 655–724 (1955), 208 references. A symposium of 19 papers by 26 authors reviewing current investigations on the disease and its therapy.

Ear, Nose, and Throat

Physiology and Anatomy.

53. "Übersicht Über die Neuroanatomie des Ohres," Ludin, von F., *Acta Oto-Laryngol.*, **45,** 207–14 (1955), no references. A short description of the neuroanatomy of all parts of the ear.

54. "The Eustachian Tube," Aschan, G., *Acta Oto-Laryngol.*, **44,** 295–311 (1954), 20 references. A review of the literature and evidence against the occurrence of tubal lymphoid tissue.

55. "The Function of the Paranasal Sinuses," Negus, V. E., *Acta Oto-Laryngol.*, **44,** 408–26 (1954), no references. A broad survey of their comparative anatomy.

56. "Physiology of the Larynx," Pressman, J. J., and Kelemen, G., *Physiol. Revs.*, **35,** 506–54 (1955), 187 references. A comprehensive review of the developments of the past 15 years.

57. "Plicae Palatinae Transversae and Pappilla Incisiva in Man," Lysell, L., *Acta Odontol. Scand.*, **13,** Suppl. 18, 5–137 (1955), 84 references. A morphologic and genetic study of the palatal rugae and incissive pappilla in the roof of the mouth with an excellent survey of the literature.

58. "Lateral Cysts and Fistulae of the Neck of Developmental Origin," Wilson, C. P., *Ann. Roy. Coll. Surgeons Engl.*, **17,** 1–26 (1955), 24 references. A thorough coverage of the subject.

59. "Technical and Surgical Anatomy of Radical Neck Dissection," Beahrs, O. H., Gossel, J. S., and Hollinshead, W. H., *Am. J. Surg.*, **90,** 490–516 (1955), 17 references. The first detailed description of the technique and surgical anatomy of a radical neck dissection which has long been relatively well standardized.

Disease.

60. "Oral Medicine," McCarthy, F. P., and McCarthy, P. L., *New Engl. J. Med.*, **252,** 1079–84, 1125–31 (1955), 59 references. A thorough review of the information which has become available during the past decade.

61. "Tonsils and Adenoids," Adin, L. E., and Singleton, J. D., *Arch. Otolaryngol.*, **59,** 351–75 (1954), 50 references. Summaries of the literature for 1952.

62. "Endoscopy," Benedict, E. B., *New Engl. J. Med.*, **252,** 709–19, 809–13 (1955), 170 references. A thorough, critical review of the recent literature.

63. "Bronchoesophagology," Putney, F. J., *Arch. Otolaryngol.*, **61,** 333–65 (1955), 148 references. Summaries of the bibliographic material available in the field of otolaryngology.

64. "Les voies aériennes supérieures et les bronches," Van de Calseyde, P., *Acta Oto-Rhin.-Laryngol. Belg.*, **8,** 425–567 (1954), 214 references. A review of the upper and lower respiratory tracts presented to the Belgian ENT Association.

65. "The Paranasal Sinuses," Salinger, S., *Arch. Otolaryngol.*, **60,** 620–29 (1954), 33 references. A review of the literature for the period July 1948 to July 1949.

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67. "Functional Examination of Hearing," Lewy, A., Shapiro, S. L., and Leshin, N., *Arch. Otolaryngol.*, **59,** 608–34 (1954), 55 references. A review of the literature for 1953.

68. "Functional Examination of Hearing," Lewy, A., Shapiro, S. L., and Leshin, N., *Arch. Otolaryngol.*, **62,** 94–110 (1955), 62 references. A review of the available literature.

69. "Die Vestibularisfunktionsprüfungen," Miehlke, A., *Fortschr. Neurol. Psychiat. u Grenzgebiete*, **23,** 73–94 (1955), 123 references.

70. "On the Renewing of the Methodology for the Stimulation of the Vestibular Apparatus," Arslan, M., *Acta Oto-Laryngol.*, Suppl. 122, 7–97 (1955), 180 references. A review of the problem of standardization of vestibular tests.

71. "The Microscope in Aural Surgery, its First Use and Later Development," Nylén, C. O., *Acta Oto-Laryngol.*, Suppl. 116, 226–40 (1954), 43 references. A "priority" review with a good description of current equipment.

72. "Anfänge und Ausbau der Otoskopie," Peyser, A., *Acta Oto-Laryngol.*, Suppl. 116, 259–70 (1954), 47 references. An historical survey of otoscopy from its beginning circa 1363.

73. "Sound Transmission in Clinical Otosclerosis," Rytzner, C., *Acta Oto-Laryngol.*, Suppl. 117, 5–137 (1954), 247 references. A study which includes a good review of the historical background and subsequent literature.

74. "The Surgical Relief of Deafness," Reading, P., *Guy's Hosp. Gaz.*, 69, 281–86 (1955), 4 references. A brief summary of an active field.

75. "The Efficacy of Nasopharyngeal Irradiation for the Prevention of Deafness in Children," Bordley, J. E., and Hardy, W. G., *Acta Oto-Laryngol.*, Suppl. 120, 5–49 (1955), 8 references. Analysis of an extensive study.

76. "The Effect of Various Operations on Hearing in Chronically Discharging Ears," Palva, T., and Sürada, U., *Acta Oto-Laryngol.*, Suppl. 116, 241–58 (1954), 40 references. A short review of the literature on mechanics of the middle ear and operative procedures in chronically discharging ears.

77. "Otitis Media and Complications," Dysart, B. R., *Arch. Otolaryngol.*, **62,** 444–55 (1955), 48 references. Summaries of pertinent articles published during 1954.

78. "The Epidemiology of Deafness Due to Maternal Rubella," Lancaster, H. O., *Acta Genet. et Statist. Med.*, **5,** 12–24 (1954), 21 references. Census and institutional data are analyzed.

Endocrinology

Physiology and Chemistry.

79. "The Hypothalamic-Endocrine System," Cleghorn, R. A., *Psychosomat. Med.*, **17,** 367–76 (1955), 77 references. A short summary of our present scanty knowledge.

80. "Bildung, Schicksal und Ausscheidung der Hypophysenvorderlappen-Hormone," Voss, H. E., *Z. Vitamin-, Hormon- u. Fermentforsch.*, **6,** 297–350 (1954), 274 references. An extensive review of the literature on the formation, fate and excretion of anterior pituitary hormones.

81. "Role of the Neurohypophysealantidiuretic-Hormone-Renal System in Everyday Clinical Medicine," Talbot, N. B., Crawford, J. D., and Kerrigan, G., *J. Clin. Endocrinol. and Metabolism*, **15,** 265–78 (1955), 4 references. A personal review.

82. "The Pituitary and Adrenals," Swingle, W. W., and Kleinberg, W., *Ann. Rev. Physiol.*, **17,** 367–92 (1955), 305 references.

83. "Adrenocortical Steroids in the Peripheral Blood of Man," Bongiovanni, A. M., and Eberlein, W. R., *J. Clin. Endocrinol. and Metabolism*, **15,** 1524–30 (1955), 31 references. A short summary of present knowledge.

84. "Aldosterone," Gaunt, R., Renzi, A. A., and Chart, J. J., *J. Clin. Endocrinol. and Metabolism*, **15,** 621–46 (1955), 126 references. A review of current knowledge of the active principle of the "amorphous fraction" of adrenal extract which is the true sodium retaining cortico-steroid.

85. "Biochemistry of the Steroid Hormones," Roberts, S., and Szego, C. M., *Ann. Rev. Biochem.*, **24,** 543–95 (1955), 406 references.

86. "Role of the Adrenal Cortex in Reproduction," Jones, I. C., *Brit. Med. Bull.*, **11,** 156–60 (1955), 45 references. An unusually clear exposition of our present knowledge.

87. "Endocrinology of Pregnancy," Amoroso, E. C., *Brit. Med. Bull.*, **11,** 117–25 (1955), 148 references. A review of our present knowledge of the subject.

88. "Biological Assay of the Gonadal and Gonadotrophic Hormones,"

Emmens, C. W., *Brit. Med. Bull.*, **11**, 135–40 (1955), 65 references. Fine summaries of these subjects.

89. "Biochemistry of the Gonadal Hormones," Callow, R. R., *Brit. Med. Bull.*, **11**, 126–30 (1955), 72 references. A brief summary.

90. "Synthetic Oestrogens," Dodds, C., *Brit. Med. Bull.*, **11**, 131–34 (1955), 16 references. A good survey of a thus far limited field.

91. "Biology of the Oestrogens," Zuckerman, S., *Brit. Med. Bull.*, **11**, 111–16 (1955), 89 references. An excellent critical summary of the subject.

92. "Endocrinology of the Testis," Parkes, A. S., *Brit. Med. Bull.*, **11**, 105–10 (1955), 69 references. A review of the literature—old and new.

93. "The Nature and Function of the Alpha Cells of the Pancreas," Korp, W., and LeCompte, P. M., *Diabetes*, **4**, 347–66 (1955), 170 references. A review of the possible role of these cells in the production of glucagon, the blood sugar raising principle.

94. "Thyroid," Barker, S. B., *Ann. Rev. Physiol.*, **17**, 417–42 (1955), 247 references.

95. "Nature, Biosynthesis and Metabolism of Thyroid Hormones," Roche, J., and Michel, R., *Physiol. Revs.*, **35**, 583–610 (1955), 200 references. An excellent review of this field.

96. "A Survey of the Factors Controlling Thyroid Function, with Especial Reference to Newer Views on Antithyroid Substances," Vanderlaan, W. P., and Storrie, V. M., *Pharmacol. Revs.*, **7**, 301–34 (1955), 238 references. A review of the newer evidence on the nature and mode of action.

97. "Some Aspects of the Comparative Biochemistry of Iodine Utilization and the Evolution of Thyroidal Function," Gorbman, A., *Physiol. Revs.*, **35**, 336–46 (1955), 88 references. A very interesting summary of scattered information.

98. "Biological Activity of Compounds Structurally Related to Thyroxine," Selenkow, H. A., and Asper, S. P., Jr., *Physiol. Revs.*, **35**, 426–74 (1955), 284 references.

99. "Hormone Thyroïdienne et Iodoprotéines Naturelles or Artificiellement Iodées," Roche, J., and Michel, R., *Actualités Pharmacol., 16e ser.*, 175–96 (1954), 101 references. A review of the thyroid hormone action of natural and synthetic iodoproteins.

Diseases.

100. "Physiopathologie der Hypophyseninsuffizienz," Sheenan, H. L., *Helv. Med. Acta.*, **22**, 324–37 (1955), 85 references. A review of the pathological physiology of pituitary insufficiency by a real authority.

101. "Cushing's Disease," Cope, O., and Raker, J. W., *New Engl. J. Med.*, **253**, 119–27, 165–72 (1955), 56 references. An analysis of the surgical experience in the care of 46 cases.

102. "Hereditary Diabetes Insipidus," Levinger, E. L., and Escamilla, R. F., *J. Clin. Endocrinol. and Metabolism*, **15**, 547–52 (1955), 15 references. A contribution to the literature on familial occurrence being evidence for 20 cases in seven generations of a family.

103. "Methods for Assessment of Adreno-cortical Function," Mason, H. L., *J. Clin. Endocrinol. and Metabolism*, **15,** 1035–38 (1955), 10 references. A short summary of the value of the present methods.

104. "Advances in Physiology of Clinical Disorders of the Adrenal Cortex," Jailer, J. W., *Advances in Internal Med.*, **7,** 125–55 (1955), 71 references. Current conceptions of clinical disorders in this field.

105. "Factors Influencing Adrenocortical Activity in Health and Disease," Bayliss, R. I. S., *Brit. Med. J.*, **II,** 495–501 (1955), 82 references. A review of clinical aspects of the subject.

106. "Management of Adrenocortical Insufficiency, "Baker, L. A., and Condon, J. V., *Med. Clin. N. Amer.*, **39,** 65–79 (1955), 44 references. A review intended for the clinician.

107. "Observations on Aldosterone in Human Urine," Luetscher, J. A., and Curtis, R. H., *Federation Proc.*, **14,** 746–51 (1955), 67 references. A review of its present status.

108. "Pheochromocytoma in Children," Smid, A. C., and DuShane, J. W., *Am. J. Diseases Children*, **90,** 81–8 (1955), 35 references. A summary of the cases reported to date.

109. "Pheochromocytoma: The Value of Certain Tests Used Routinely in Diagnosis," Orgain, E. S., *Ann. Internal Med.*, **43,** 1178–94 (1955), 81 references. A critical review of the diagnostic tests proposed for use in this condition.

110. "The Use of Radioactive Iodine in the Diagnosis and Treatment of Hyperthyroidism: Ten Years' Experience," Chapman, E. M., and Maloof, F., *Medicine*, **34,** 261–321 (1955), 170 references. An excellent summary of the subject and literature for the years before 1953.

111. "Considérations cliniques sur l'hyperfonction thyroïdienne," Vannotti, A., *Helv. Med. Acta*, **21,** 313–28 (1954), 39 references. A brief review of the clinical aspects of hyperthyroidism.

112. "Therapie der Hyperthyreosen," Bansi, H. W., *Helv. Med. Acta*, **21,** 329–47 (1954), 33 references. A review of the current status of the therapy of hyperthyroidism.

113. "Hyperthyroidism," Rawson, R. W., *Disease-a-Month*, 3–43, (April, 1955), 49 references. An excellent short clinical survey.

114. "Investigation of Diseases of the Thyroid Gland by Means of Radioactive Iodine," Owen, C. A., McConahey, W. M., Keating, F. R., Jr., and Orvis, A. L., *Federation Proc.*, **14,** 723–27 (1955), 8 references. An evaluation of tests using radioiodines for clinical diagnosis of thyroid disease.

115. "Thyroiditis: A Review," Hazard, J. B., *Am. J. Clin. Pathol.*, **25,** 289–300, 399–426 (1955), 155 references. An excellent review of all phases of the subject.

116. "Chronic Thyroiditis and Riedel's Struma: Etiology and Pathogenesis," Goetsch, E., and Kamner, M., *J. Clin. Endocrinol. and Metabolism*, **15,** 1010–34 (1955), 71 references. A comprehensive review of the extensive literature accompanying a report of new cases and information.

117. "Problems of Impotence in Aging Males," Kelly, G. L., *J. Am.*

Geriat. Soc., **3,** 883–89 (1955), 17 references. A brief but extremely useful review by the authority in this field.

118. "The Surgery of Male Subfertility," Hanley, H. G., *Ann. Roy. Coll. Surgeons Engl.*, **17,** 159–83 (1955), 41 references. A well illustrated review of the problem.

EYE

Physiology.

119. "The Physiology of Vision," Willmer, E. N., *Ann. Rev. Physiol.*, **17,** 339–66 (1955). 257 references.

120. "Optics and Visual Physiology," Miles, P. W., *Arch Ophthalmol.*, **53,** 893–914 (1955), 278 references. A review of the literature for 1954.

121. "Dies Histologie Struktur der ausseren Augenmuskeln als Ausdruck ihrer Function," Siebeck, R., and Krüger, P., *Albrecht von Graefe's Arch. Ophthalmol.*, **156,** 639–52 (1955), 78 references. A summary of the comparative anatomy and function of the eye muscles.

122. "The Absolute Threshold of Vision," Weale, R. A., *Physiol. Revs.*, **35,** 233–46 (1955), 49 references. A basic review.

123. "Die ontogenetische Entwicklung des Helligskeits und Farbensehens beim Menschen," Trincker, D., and Trinker, I., *Albrecht von Graefe's Arch. Ophthalmol.*, **156,** 519–34 (1955), 66 references. Includes a good survey of the literature on the development of color sense.

124. "Physiologic Chemistry of the Eye," Sallmann, L., *Arch. Ophthalmol.*, **52,** 604–40 (1954), 162 references. A survey of papers published during 1953.

125. "Physiological Chemistry of the Eye," Sallmann, L., *Arch. Ophthalmol.*, **54,** 605–35 (1955), 188 references. A review of pertinent articles published during 1954.

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126. "Familial Primary Hypoplasia of the Orbital Margin," Urrets-Zavalia, A., *Trans. Am. Acad. Ophthalmol. Otolaryngol.*, **59,** 42–59 (1955), 45 references. A review of a new developmental disorder.

127. "The Orbit," Devoe, A. G., *Arch. Opthalmol.*, **54,** 438–61 (1955), 328 references. A careful review of the literature for 1954.

128. "The Orbit," Devoe, A. G., *Arch. Opthhalmol.*, **52,** 461–89 (1954), 305 references. A critical review of the literature for 1953.

129. "Diagnosis and Treatment of Orbital Tumours," Foster, J., *Ann. Roy. Coll. Surgeons Engl.*, **17,** 114–29 (1955), 22 references. An excellent summary of the practical aspects.

130. "Strabismus," Wheeler, M. C., *Arch. Ophthalmol.*, **54,** 100–34 (1955), 139 references. A careful review of the recent literature.

131. "Vital Staining of Conjunctiva and Cornea," Passmore, J. W., and King, J. H., *Arch. Opthhalmol.*, **53,** 568–74 (1955), 19 references. A review of the literature in connection with a critical study.

132. "Combined Ocular and Cutaneous Manifestations of Disease,"

Allende, M. F., and Thygeson, P., *Postgrad. Med.*, **17,** 192–202 (1955), no references. An "exhibit" summary shown photographically.

133. "Glaucoma," Haas, J. S., *Arch. Ophthalmol.*, **54,** 941–56 (1955), 194 references. A review of the literature for 1954–55.

134. "Physiological and Pharmacological Influences upon Intraocular Pressure," Grant, W. M., *Pharmacol. Revs.*, **7,** 143–182 (1955), 203 references. A thorough survey of current and recent investigations into the control of intraocular pressure particularly with respect to the action of drugs.

135. "Symposium: Congenital Glaucoma," Shaffer, R., Scheie, H. G., Barkan, O., Haas, J. S., and Meyer, S. J., *Trans. Am. Acad. Ophthalmol.*, **59,** 297–345 (1955), 118 references. Those facts which seem established and clinically important are well organized and reviewed in a series of five papers.

136. "The Importance of Glaucoma with Increasing Age," Berens, C., and Breakey, A. S., *J. Am. Gerait. Soc.*, **3,** 181–96 (1955), 29 references. An excellent summary of the subject.

137. "Retinal and Conjunctival Vascular Changes in Normal and Toxemic Pregnancy," Landesman, R., *Bull. N. Y. Acad. Med.*, **31,** 376–90 (1955), 34 references. A short clinical summary of the subject.

138. "Cornea and Sclera," Gundersen, T., *Arch. Ophthalmol.*, **53,** 271–300 (1955), 298 references. An excellent review of the literature for 1954.

139. "Lids, Lacrimal Apparatus, and Conjunctiva," Braley, A. E., *Arch. Ophthalmol.*, **53,** 119–41 (1955), 190 references. A review of the pertinent literature for 1954.

140. "Ätiologische Diagnostik der Uveitis," Witmer, R. H., *Albrecht von Graefe's Arch. Ophthalmol.*, **156,** 235–60 (1955), 81 references. Includes the literature on clinical and experimental work in man and animals.

141. "Diseases of the Uveal Tract," Calhoun, F. P., *Arch. Ophthalmol.*, **53,** 437–55 (1955), 165 references. A review of papers published from October, 1953, to October, 1954.

142. "Persistent Hyperplastic Primary Vitreous," Reese, A. B., *Trans. Am. Acad. Ophthalmol. Otolaryngol.*, **59,** 271–96 (1955), 46 references. A review of persistent tunica vasculosa lentis or persistent posterior fetal fibrovascular sheath of the lens.

143. "The Medical Significance of Lenticular Opacities (Cataract) Before the Age of Fifty," Meyer, R. J., *New Engl. J. Med.*, **252,** 622–28 (1955), 210 references. A detailed review with emphasis on their occurrence in systemic disorders.

144. "Retrolental Fibroplasia," Cook, C. G., *Guy's Hosp. Gaz.*, **69,** 67–74 (1955), 3 references. An illustrated usable clinical summary.

145. "Symposium: Retrolental Fibroplasia (Retinopathy of Prematurity)," Owens, W. C., Friedenwall, J. S., Silverman, W. A., Kinsey, V. E., Hemphill, F. M., Patz, A., Blodi, F. C., and Reese, A. G., *Trans. Am. Acad. Ophthalmol. Otolaryngol.*, **59,** 7–41 (1955), 36 references. A symposium covering the present status of this disease.

146. "Diseases of the Retina and Optic Nerve," Wagener, H. P., *Arch.*

Ophthalmol., **53**, 722–54 (1955), 232 references. The literature for 1954 is reviewed.

147. "Klinische Studie zur Retinitis diabetica proliferans," Fischer, F., *Albrecht von Graefe's Arch. Ophthalmol.*, **156**, 552–60 (1955), 56 references. A good summary of the literature.

148. "Zur Ätiologie der Neuritis retrobulbaris," Eckstein, von H., *Confinia Neurol.*, **14**, 8–26 (1954), 33 references. A review of 356 cases observed in the Basel University Eye Clinic over a 20-year period.

149. "Neuro-Ophthalmology," Payne, F., *Arch. Ophthalmol.*, **52**, 781–806 (1954), 80 references. A careful review of the literature for 1953.

150. "Neuro-Ophthalmology," Payne, F., *Arch. Ophthalmol.*, **54**, 763–88 (1955), 78 references. Important recent papers are well reviewed.

151. "Typical Total Color Blindness Reinterpreted," Walls, G. L., and Heath, G. G., *Acta Ophthalmol.*, **32**, 253–97 (1954), 43 references. A review of the authors' hypothesis.

Gastrointestinal Tract

Physiology.

152. "The Digestive System," Steggerda, F. R., *Ann. Rev. Physiol.*, **17**, 129–54 (1955), 167 references.

153. "Chemical Evaluation of the Functions of the Liver," Reinhold, J. G., *Clin. Chem.*, **1**, 351–421 (1955), 437 references. An excellent and clinically useful review.

154. "Recent Developments in our Knowledge of Bile Salts," Haslewood, G. A. D., *Physiol. Revs.*, **35**, 178–196 (1955), 166 references. A relatively brief but complete review of the literature.

155. "Acid Formation and Acidity Control in the Stomach," Heinz, E., and Öbrink, K. J., *Physiol. Revs.*, **34**, 643–73 (1954), 247 references. A review of a muddled field which takes an independent route in advocating ideas.

156. "Gastric Urease," Kornberg, H. L., and Davies, R. E., *Physiol. Revs.*, **35**, 169–177 (1955), 87 references. A review of the literature.

Disease—General.

157. "Abdominal Surgery," Welch, C., *New Engl. J. Med.*, **253**, 1068–74, 1116–21 (1955), 112 references. A review of papers in this field which have been outstanding or indicative of particular trends and have appeared during the past two years.

158. "Acute Abdominal Pain," Rukstinant, G. J., *Am. J. Proctol.*, **6**, 228–38, 319–25 (1955), 41 references. A review of the subject when it is due to dissecting aortic aneurysms.

159. "Present-Day Problems in Nonpenetrating Abdominal Trauma," Estes, W. L., *Bull. Am. Coll. Surgeons*, **39**, 11–18 (1955), 9 references. A brief survey of measures available to combat high mortality.

160. "Lawson Tait—Father of Abdominal Surgery," Tomkinson, J. S.,

Guy's Hosp. Gaz., **69,** 371–75 (1955) 4 references. A brief survey of his life and influence.

161. "Twenty-five Years of Progress in the Treatment of Acute Peritonitis," Orr, T. G., *Am. Surgeon*, **21,** 873–86 (1955), 59 references. A summary of the advancements made.

162. "Revue des travaux argentine de Gastroentérologie (1951–54)," Royer, M., and Mazure, R. A., *Gastroenterologica*, **83,** 295–311 (1955), 181 references. A review in French of the recent Argentine work in gastroenterology.

Disease—Hemorrhage.

163. "Gastrointestinal Bleeding," Warthin, T. A., *Disease-a-Month*, 1–40 (December, 1954), 7 references. A review of the newer methods of control.

164. "Management of Massive Gastrointestinal Hemorrhage on the Wards of the Boston City Hospital," Zamcheck, N., *Arch. Internal Med.*, **96,** 78–89 (1955), 27 references. A critical assay of present day methods.

165. "Diagnostic et Traitment des Hémorragies digestive aiguës," Moyson, F., and de Scovill, A., *Acta Chir, Belg.*, Suppl. 1, 1–144 (1955), 29 references. A survey of the various aspects of acute hemorrhage from the gastro-intestinal tract including causes, diagnoses, pathologenesis, pathologic anatomy, and therapy.

166. "Gastrointestinal Hemorrhage (Excluding Peptic Ulcer and Esophageal Varices)," Brick, I. B., and Jeghers, H. J., *New Engl. J. Med.*, **253,** 458–66, 511–18, 555–60 (1955), 160 references. Points up representative trends in the literature.

Disease—Stomach.

167. "Peptic Ulcer," Ruffin, J. M., and Carter, D. D., *Disease-a-month*, 3–32 (August, 1955), 15 references. All phases of this disease are briefly reviewed.

168. "Changes in the Surgical Treatment of Peptic Ulcer over a twenty-five Year Period," Walters, W., *Am. Surgeon*, **21,** 641–52 (1955), 27 references. A critical review of the subject.

169. "Mechanism of Pain in Peptic Ulcer: A Reply," Palmer, W. L., *Am. J. Med.*, **18,** 513–18 (1955), 20 references. An effort is made to prove that the pain of peptic ulcer is due to hyperacidity.

170. "Acute Mucosal Lesions of the Stomach: A Study of Gastrectomy Specimens," Fodden, J. H., *Medicine*, **34,** 233–55 (1955), 53 references. A re-investigation of the place of gastritis in ulcer etiology and other aberrances in the peptic mucosa in ulcer disease.

171. "The Late Complications of Gastrectomy," Wells, C., *Ann. Roy. Coll. Surgeons Engl.*, **16,** 145–62 (1955), 12 references. An unusually good clinical review.

172. "Les diverticules gastriques," Laurent, Y., and Brombart, M.,

Acta Gastro-Enterol. Belg., **17**, 262–79 (1954), 44 references. A review of the literature plus six new cases of gastric diverticula. The authors critically consider the etiology of the disease.

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Disease—Lower Bowel.

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516. "Relation of Structure to Function of the Tissues," Burton, A. C., *Physiol. Revs.*, **34,** 619–42 (1954), 55 references. A successful effort has been made to present ideas rather than review all pertinent literature.

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A study of primary malignant tumors of the small intestine based on 795 cases described in the literature.

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539. "Breast Cancer and Pregnancy or Lactation," Lewison, E. F., *Intern. Abstr. Surg.*, **99,** 417–24 (1954), 25 references. A statistical review of the literature.

540. "The Problem of Prognosis in Cancer of the Breast," Lewison, E. F., *Surgery*, **37,** 479–506 (1955), 82 references. A very critical review of the author's data and pertinent literature.

541. "Treatment of Cancer of the Breast Showing 25 Years of Progress," Gould, E. A., and Kerr, H. H., *Am. Surgeon*, **21,** 865–72 (1955), 37 references A review of diagnosis and management of this disease.

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573. "Convulsive Disorders," Carter, S., and Merritt, H. H., *Disease-a-Month*, 3–40 (December, 1955), 43 references. An excellent clinical résumé.

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27 references. A review of recent literature on the diagnosis and treatment of cerebral abscesses which emphasizes the improved prognosis.

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718. "Hauttuberkulose," Kroepfli, P., *Dermatologica*, **111,** 168–76 (1955), 65 references. A review of the literature from July, 1954 to June, 1955 on tuberculosis of the skin (See 724).

719. "Pruritus, Pruigo, Neurodermitis, Lichenruber," Mali, J. W. H., *Dermatologica*, **109,** 31–36 (1954), 60 references. Literature for the year 1953 is summarized.

720. "Acne vulgaris, Rosacea, Seborrhoe, Psoriasis, Parapsoriasis, Erythematodes," Schuppli, R., *Dermatologica*, **109,** 37–46 (1954), 98 references. A review of the literature for 1952.

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724. "Hauttuberkulose," Kroepfli, P., *Dermatologica*, **109,** 252–72 (1954), 136 references. Review of the literature from June, 1952 to June, 1954 on skin tuberculosis (See 718).

725. "Anlageanomalien," Lutz, W., *Dermatologica*, **110,** 91–96 (1955), 78 references. An excellent summary of recent contributions concerning vestigial anomalies in the skin.

726. "Tumoren," Lutz, W., *Dermatalogica*, **110,** 398–404 (1955), 88 references. Recent literature on skin tumors is covered with brief but critical summaries.

727. "Veranderungen im Pigmentgehalt und an den Anhangsorganen," Lutz, W., *Dermatologica*, **111,** 111–13 (1955), 33 references. A brief review of recent literature on changes in the pigment content and the accessory organs of the skin.

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729. "Akute Infektionskrankheiten," Lutz, W., *Dermatologica*. **111,** 125–28 (1955), 60 references. A review of recent literature on acute infectious diseases of the skin.

730. "Some Aspects of Dermatology in Neurology," Beerman, H., *Am. J. Med. Sci.*, **230,** 441–64 (1955), 145 references. An excellent survey of the literature.

731. "Fortschritte auf den Grenzgebieten der Neurologie und Dermatologie," Thies, W., and Keilig, W., *Fortschr. Neurol. Psychiat. u. Grenzgebiete*, **23**, 496–532 (1955), 464 references.

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THERAPEUTICS

Antibiotics—general.

740. "The Current Status of the Development of Antimicrobial Agents," Hobby, G. L., *Bull. N. Y. Acad. Med.*, **31**, 181–97 (1955), 26 references. A short review of the larger phases of the problem.

741. "Antibiotics," Eagle, H., and Saz., A. K., *Ann. Rev. Microbiol.*, **9**, 173–226 (1955), 408 references.

742. "Biochemistry of Antibiotics," Binkley, S. B., *Ann. Rev. Biochem.*, **24**, 597–626 (1955), 284 references.

743. "Chemistry of Antibiotics of Clinical Importance," Regna, P. P., *Am. J. Med.*, **18**, 686–716 (1955), 303 references. An excellent review of the literature covering the less highly specialized chemical aspects.

744. "Die neuere Entwicklung der Antibiotica als Arzneimittel,"

Büchi, J., *Antibiotica et Chemotherapia*, **1**, 1–45 (1954), 40 references. The recent development of antibiotics as therapeutic agents. A thorough review of the subject.

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746. "Klinische Probleme der Antibiotica-Therapie," Apell, O., *Antibiotica et Chemotherapia*, **2**, 1–33 (1955), 74 references. A clinical review.

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752. "Chemotherapeutic and Antibiotic Drugs in the Management of Infections of the Urinary Tract," Kass, E. H., *Am. J. Med.*, **18**, 764–81 (1955), 98 references. An assessment of the current situation.

753. "Heutiger Stand der antibiotischen und chemotherapeutischen Behandlung der Geschlechtskrankheiten," Fischer, E., *Antibiotica et Chemotherapia*, **2**, 233–300 (1955), 508 references.

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762. "Les Accidents provoqués par les antibiotiques," Rentchnick, P., *Antibiotica et Chemotherapia*, **1**, 96–179 (1954), 335 references. A review of the literature reporting undesirable side effects of antibiotics.

763. "Accidents liés à la médication antibiotique," Cheymol. J., *Arztl. Forsch.*, **5**, 1–9 (1955), 56 references. A short review of undesirable side reactions sometimes produced by antibiotics.

764. "Complications of Antibiotic Therapy," von Oettingen, W. F., *Am. J. Med.*, **18**, 792–809 (1955), 214 references. A timely review of all aspects of the subject based on an extensive literature.

765. "Untoward Reactions to Antibiotics," Kagan, B. M., and Faller, L., *Med. Clin. N. Amer.*, **39**, 111–24 (1955), 104 references. A good summary from the literature.

766. "Cutaneous and Serologic Tests in Allergy to Antibiotics," Pirila, V., *Antibiologica et Chemotherapia*, **2**, 207–32 (1955), 75 references. A review of the literature which shows such variable results that nothing definite can be concluded about the basic immunology of the reactions to antibiotics.

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771. "Bacterial Resistance," Bryson, V., and Demerec, M., *Am. J. Med.*, **18,** 723–37 (1955), 90 references. An excellent review which raises many questions for the future.

772. "Microbial Drug Resistance," Bryson, V., and Szybalski, W., *Advances in Genet.*, **7,** 1–46 (1955), 138 references. For the microbiologist.

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776. "Present Status of the Chemotherapy of Tuberculosis," Ebert, R. H., *Am. J. Med.*, **18,** 738–52 (1955), 106 references. A good summary of the present situation.

777. "Problems of Chemotherapy in the Older Age Group," Lehr, D., *J. Am. Geriat. Soc.*, **3,** 355–66 (1955), 41 references. A summary which is actually applicable to any age group.

778. "Approaches to the Chemotherapy of Viral Diseases," Horsfall, F. L., Jr., *Bull. N. Y. Acad. Med.*, **31,** 783–93 (1955), 33 references. A critical personal consideration of the problem.

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ACTH and Cortisone Derivatives.

780. "L'A.C.T.H. et La Cortisone dans le Traitment des Maladies Allergiques Respiratoires," Vallery-Radot, P., Laroche, P., and Milliez, P., *Acta Allergol.*, **7,** 14–49 (1954), 100 references. A résumé of the recent literature.

781. "Treatment of Acute Rheumatic Fever in Children," Joint Report, *Brit. Med. J.*, **I,** 555–74 (1955), 6 references. A summary of a co-operative clinical trial of ACTH, Cortisone, and Aspirin which showed remarkable little difference in the end results with the various types of therapy.

782. "Corticotropin and Cortisone in Rheumatoid Arthritis," Fischer, F., *Acta Med. Scand.*, Suppl. 305, 15–268 (1955), 754 references. A survey of the literature and evaluation of this therapy.

783. "The Present Status of ACTH and Adrenal Steroid Therapy in Medicine," Beck, J. C., *Ann. Internal Med.*, **43,** 667–84 (1955), 16 references. A practical consideration of this field.

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Steroids in Systemic Disease, 8 papers by 25 authors on Selected parenteral Forms of Hydrocortisone in Therapy, 7 papers by 10 authors on the Topical Use of Hydrocortisone on the skin, eyes and nasopharynx, and 7 papers by 19 authors on Halogenated Analogs of Hydrocortisone.

785. "The Role of ACTH, Cortisone and Hydrocortisone in Surgery," Abbott, W. E., Krieger, H., and Levey, S., *Ann. Internal Med.*, **43,** 702–30 (1955), 222 references. A good review of the literature.

786. "Cortisone, ACTH and Infection," Thomas, L., *Bull. N. Y. Acad. Med.*, **31,** 485–99 (1955), 23 references. A general treatment of the subject which raises many provocative ideas.

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789. "Rapports de Structure entre Sympathomimétiques et Sympatholytiques de l'Adrénaline a l'Ergotamine," Bovet, D., and Bovet-Nitti, F., *Actualités Pharmacol., 16e ser.*, 21–50 (1954), 145 references. A review of the relation of the structure of epinephrine and ergotamine and their sympathomimetic and sympatholytic actions.

790. "Analyse Physicochimique de l'Action des Anesthésiques Locaux," Charonnat, R., *Actualités Pharmacol., 16e ser.*, 71–113 (1954), 194 references. A review of the relation of their physical chemical properties to the action of local anesthetics.

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792. "Organic Metal Co-ordinate Compounds," Bergy, G. A., *Am. J. Pharmacol.*, 126, 198–216 (1954), no references. An interesting survey of chelating compounds.

793. "Phloroglucin-Derivate als Inhaltsstoffe wurmwirksamer Drogen," Zinner, G., *Arztl. Forsch.*, **5,** 123–27 (1955), 37 references. A review of phloroglucine derivatives as ingredients of anthelminic drugs.

794. "The Present Status of Therapeutic Use of Enzymes," Clifton, E. E., *Am. J. Med. Sci.*, **228,** 568–85 (1954), 290 references. A brief summary of the subject.

Addiction.

795. "Opium Production and Control," Evcim, N. N., *Am. J. Pharmacol.*, **126,** 40–56 (1954), 19 references. An excellent brief survey of the problem.

796. "Medical Aspects of Opiate Addiction," Isbell, H., *Bull. N. Y. Acad. Med.*, **31,** 886–901 (1955), 25 references. A broad survey of the subject.

797. "Nutrition as a Factor against Addiction," Verzár, F., *Am. J. Clin. Nutrition*, **3,** 363–74 (1955), 61 references. A critical survey of the problem of coca chewing in South America.

798. "Morphin-Antagonisten," Untercharnscheidt, F., *Arztl. Forsch.*, **5,** 630–34 (1955), 46 references. A brief review of the literature on antagonists to morphine.

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799. "The Pharmacology of Vascular Smooth Muscle," Furchgott, R. F., *Pharmacol. Revs.*, **7,** 183–263 (1955), 355 references. A review of the literature through November, 1954 primarily concerned with the local actions of drugs.

800. "Blood Pressure Reduction in Arterial Hypertension by Hexamethonium and Pentapyrrolidinium Salts," Smirk, F. H., *Am. J. Med.*, **17,** 839–50 (1954), 90 references. A critical review of the literature in the light of the author's broad experience in this field.

801. "Hypotensive Drugs," Douthwaite, A. H., *Guy's Hosp. Gaz.*, **69,** 354–60 (1955), no references. A fine critical survey on a few pages.

802. "Die Erforschung der Rauwolfia-Alkaloide von ihren Anfängen bis zur Gegenwart," Schneider, W., *Arztl. Forsch.*, **5,** 666–72 (1955), 64 references. A review of the historical development of the chemistry of Rauwolfia.

803. "Action of Drugs on Carotid Body and Sinus," Heymans, C., *Pharmacol. Revs.*, **7,** 119–42 (1955), 264 references. A careful review by a master of this field.

804. "Bioflavonoids and the Capillary," Martin, G. J., and Szent-Györgi, A., *et al.*, *Ann. N. Y. Acad. Med.*, **61,** 637–735 (1955), 222 references. A symposium of 13 papers by 17 authors which makes a great effort to elevate the questionable therapeutic usefulness of these compounds.

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806. "Help from Digitalis," Baker, C., *Guy's Hosp. Gaz.*, **69,** 215–22 (1955), no references. A more useful summary than most more wordy ones.

807. "Les Antifibrillants Cardiaques," Bijlsma, U. G., *Actualités Pharmacol., 16e ser.*, 1–19 (1954), 51 references. A brief review of the theories of fibrillation and action of antifibrillant drugs.

808. "The Question of Reactions to Mercurial Diuretics," Brown, E. A., *Ann. Allergy*, 13, 131–59 (1955), 105 references. A reappraisal of the subject and relevant literature.

Eye and Ear.

809. "Pharmacology and Toxicology," Harris, J. E., *Arch. Ophthalmol.*, **52,** 275–327 (1954), 664 references. A review of the literature for 1953 with special attention to ophthalmology.

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812. "The Ototoxicity of Drugs," Lurie, M. H., *Trans. Am. Acad. Ophthalmol. Otolaryngol.*, **59,** 111–17 (1955), 15 references. A brief summary of deafness due to drugs.

813. "Recent Trends in Nasal Medication," Neffson, A. H., *Am. J. Med. Sci.*, **228,** 465–68 (1954), 12 references. A very short survey.

814. "The Physiological Approach to Nasal Medication," Fabricant, N. D., *Am. J. Med. Sci.*, **230,** 436–40 (1955), 10 references. A brief critical survey.

Nervous System.

815. "Die Weckamine," Soehring, K., Hardebeck, K., and Schröder, L., *Arztl. Forsch.*, **5,** 42–48 (1955), 176 references. [*Arztl. Forsch.*, **4,** 507 (1954) covers the Anglo-American work]. The German speaking literature on the chemistry, pharmacology ane clinical action of the analeptic amines is carefully reviewed.

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817. "The Current Drug Therapy of Epilepsy," Drake, F. R., *Am. J. Med. Sci.*, **230,** 98–107 (1955), 69 references. A critical review of the literature.

818. "Use of the Dione Drugs (Propazone, Tridione, Paradione, Dimedione and Malidone) in the Treatment of Epilepsy of Children," Livingston, S., and Boks, L. L., *New Engl. J. Med.*, **253,** 138–43 (1955), 68 references. A routine summary of recent reports.

819. "Reserpine in the Treatment of Neuropsychiatric, Neurological and Related Clinical Reports," Yonkman, F. F., Mohr, F. L., and Graeme, J. L., *et al.*, *Ann. N. Y. Acad. Med.*, **61,** 1–280 (1955), 265 references. A symposium of 31 papers by 57 authors dealing almost entirely with clinical usage.

820. "Structure Fonctionelle du Système Neurovégétatif et Points d'attaque des Alcaloïdes de l'Ergot de Seigle," Rothlin, E., *Actualités Pharmacol., 16e ser.*, 197–219 (1954), 45 references. A concise review of the effect of the parasympathetic and sympathetic nervous systems upon various tissues and organs and the action of the ergot alkaloids thereon.

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Miscellaneous.

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823. "Application of Homeostatic Principles to the Practice of Parental Fluid Therapy," Talbot, N. B., Herrigan, G. A., Crawford., J. D., Cochran, W., and Terry, M., *New Engl. J. Med.*, **252,** 856–62, 898–906 (1955), 21 references. A concise discussion of the problem with a clinical point of view.

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825. "Symposium on the Antimetabolites—Their Modes of Action and Therapeutic Implications," Goodhart, R. S., Cerecedo, L. R., Lambooy, J. P., Umbreit, W. W., Bird, O. P., Wittle, E. L., Thompson, R. Q., McGlohon, V. M., Woolley, D. W., Burchenal, J. H., Hitchings, G. H., and Hove, E. L., *Am. J. Clin. Nutrition*, **3,** 271–336 (1955), 335 references. A collection of eight articles reviewing current knowledge of various vitamin antagonists.

826. "Histamine Metabolism," Paton, W. D., *Intern. Arch. Allergy and Appl. Immunol.*, **6,** 203–29 (1955), 54 references. An excellent discussion of the subject in its broadest aspects.

Toxicology

827. "Threshold Limit Values for 1955" (Report by Committee for Governmental Industrial Hygienists), Ball, W. L., Fairhall, L. T., Kay, K., Stokinger, H. E., Vorwald, A. J., Weller, L. F., and Coleman, A. L., *Arch. Ind. Hyg. and Occupational Med.*, **11,** 521–24 (1955), references "on request" on each substance. The usual annual list of toxicity levels.

828. "The Metabolism and Toxicity of Methanol," Röe, O., *Pharmacol. Revs.*, **7,** 399–412 (1955), 54 references. A review of the literature—old and new.

829. "A Critical Evaluation of Fluoridation," Brusch, C. A., and Ceresia, G. B., *Am. J. Pharmacol.*, **126,** 373–87 (1954), 39 references. Faulty arguments against fluoridation of water supplies.

830. "Comparative Response of Insects and Mammals to Certain Halogenated Hydrocarbons Used as Insecticides," Winteringham, E. P. W., and Barnes, J. M., *Physiol. Revs.*, **35,** 701–739 (1955), 335 references. A review of a subject which determines the practical usefulness of these compounds.

Urinary System

Physiology.

831. "Anatomy of the Glomerulus," Mueller, C. B., Mason, A. D., Jr., and Stout, D. G., *Am. J. Med.*, **18,** 267–76 (1955), 24 references. An excellent review of the histology of this unit.

832. "Nouveaux procédés d'exploration fonctionelle des reins," Traeger, J., *Helv. Chir. Acta.*, **21,** 137–54 (1954), 21 references. A review of new procedures for the study of renal function.

833. "Patterns of Protein Excretion by the Kidneys," King, S. E., *Ann. Internal Med.*, **42,** 296–323 (1955), 51 references. A study of the subject.

834. "The Metal Chelate Compounds of Urine," Boyce, W. H., Garvey, F. K., and Norfleet, C. M., Jr., *Am. J. Med.*, **19,** 87–95 (1955), 26 references. A study of the relation of the organic matrix to the origin of urinary calculi.

Diseases.

835. "Urology—From 1905 to 1955," Higgins, C. C., *Intern. Abstr. Surg.*, **101,** 1–40 (1955), 368 references. An interesting and useful review of a specialty which although it has existed in a way has really become adult during the period under survey.

836. "Urinary Tract Infections, Jawetz, E., *Disease-a-Month*, 3–31 (November, 1954), 7 references. A working clinical summary of the subject.

837. "Pathogenesis and Treatment of Renal Lithiasis—Newer Concepts," Butt, A. J., *Advances in Internal Med.*, **7,** 11–32 (1955), 56 references. A survey of all the evidence supporting a unique new theory.

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